A.M.A. Archives of
OPHTHALMOLOGY

FEBRUARY 1956

VOLUME 55 NUMBER 2

Observations on Ocular Pigment and Pigmentation *Alfred Cowan*

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George T. Tani, Kenneth N. Ogle, Rex W. Weaver, and Theodore G. Martens

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E. S. Palmerton

Ocular Involvement in Multiple Myeloma *Melvin Bronstein*

Perfusion Studies on the Outflow of Aqueous Humor in Human Eyes
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Human Chorioretinal Burns from Atomic Fireballs
H. W. Rose, David V. L. Brown, Victor A. Byrnes, and Paul A. Cibis

Experimental Approach to the Pathogenesis of Retrolental Fibroplasia *Bo E. Hellström*

Necroscleritis Nodosa *Manos A. Petrohelos and J. Reimer Wolter*

Tests for Color Deficiency Based on the Pseudoisochromatic Principle *Louise L. Sloan and Adelaide Habel*

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Use of Nylon Thread and Polyethylene Tubing in Nasolacrimal Duct Stenosis *A. B. Vicencio*

Cornea and Sclera *Trygve Gundersen*

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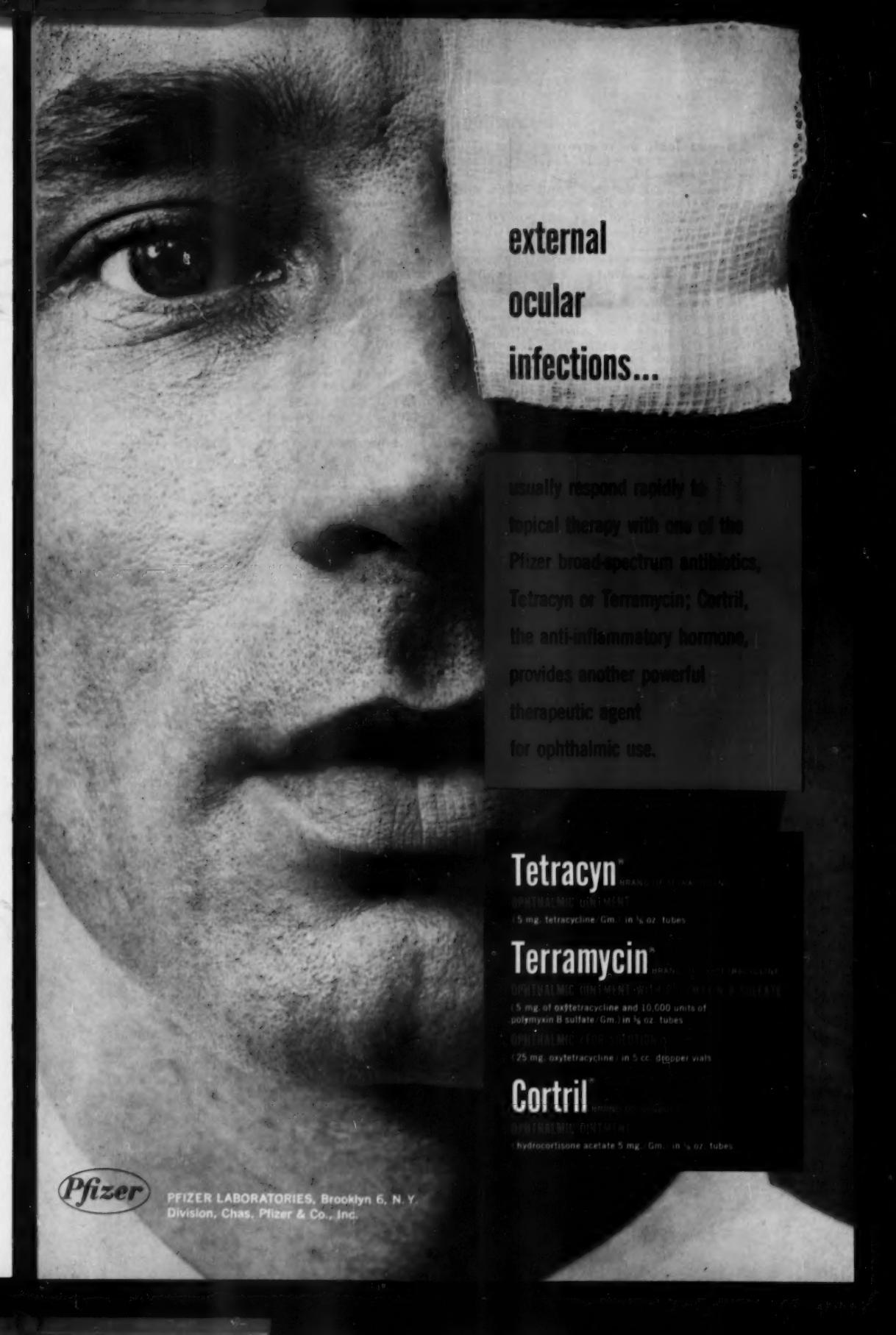
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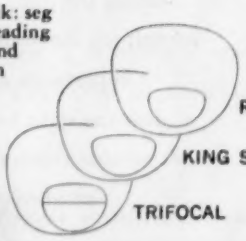

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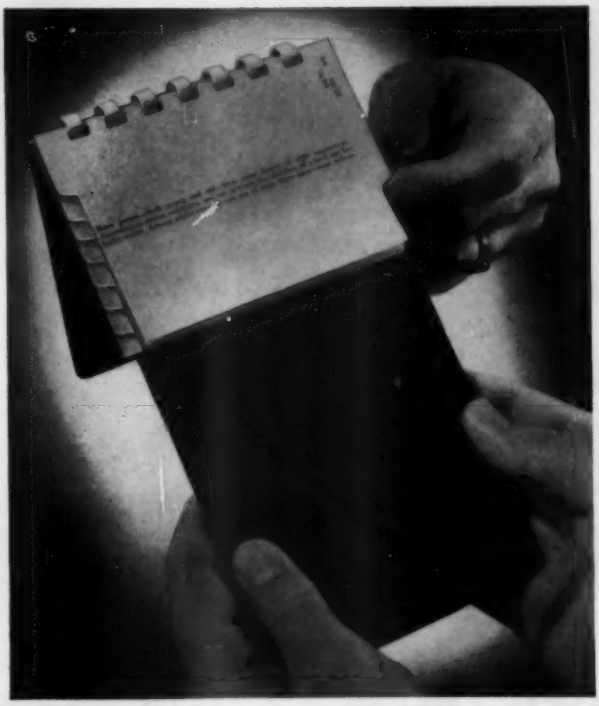

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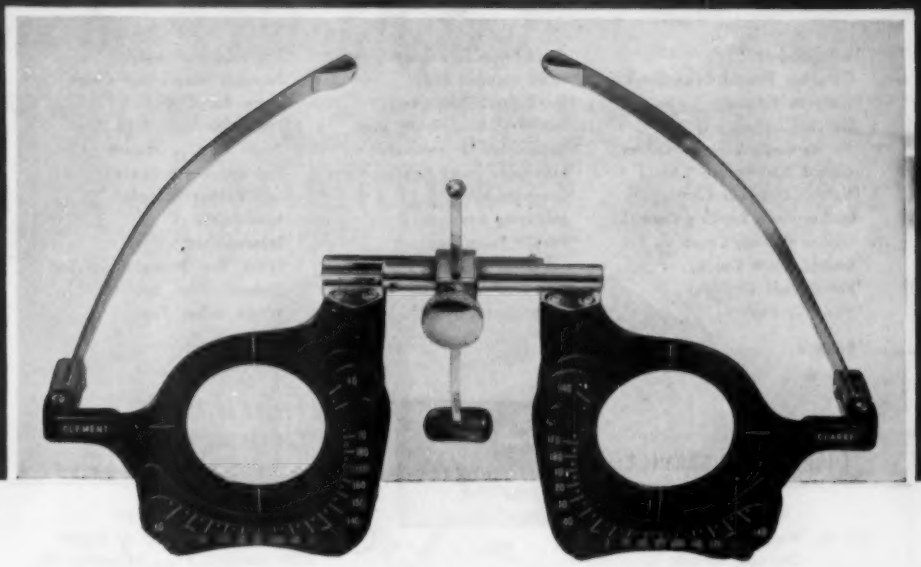

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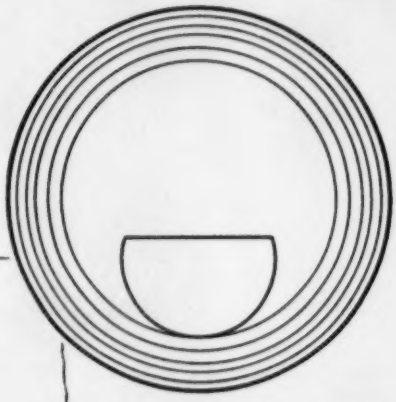

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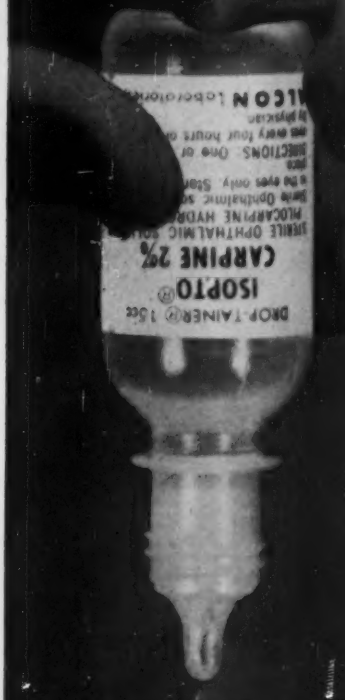

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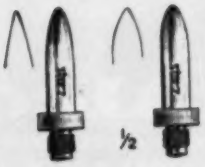

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Observations on Ocular Pigment and Pigmentation

Eighteenth Annual de Schweinitz Lecture

ALFRED COWAN, M.D., Philadelphia

I should like to be able to express adequately my deep and sincere appreciation of this honor. I am gratified beyond words to have been invited to deliver this de Schweinitz Lecture; but mingled with this feeling is a heavy sense of the responsibility involved. I want to take this opportunity to pay my personal tribute to the memory of Dr. de Schweinitz. He was a fine gentleman, always surrounded by an aura of greatness. It is not enough to say that he was an eminent ophthalmologist. He was a preeminent man who chose to be an ophthalmologist. He showed me many kindnesses during the time I knew him and worked under him, and I feel especially indebted for his having chosen me to assist Basil Graves, whom he brought over from England to give a number of short courses in slit lamp microscopy. It was in the earliest days of the then newest method of clinical investigation, and through him I was among the first in America to be initiated into the technique of biomicroscopy. I mention this because a large part of my presentation tonight consists of observations and deductions based on the slit lamp microscopic examinations of actual cases seen in clinics and private practice over a long period of time.

The term "pigment" is sometimes erroneously used to imply that it has the same meaning as color, or even that the sensation of color is solely produced by pigments or pigmentation. We should not forget that color is a sensation, produced by light radiated from a luminous body or reflected from the surface of a nonluminous body, the result of various stimuli, physical, physiologic, and psychologic, among which may be mentioned the transmission of selective light through colored glass and other transparent media, and analysis of the spectral or primary colors by dispersion of light passing through a prism, by diffraction, scattering, interference, and other phenomena. It can also be produced in other ways, such as an electric shock. It is far from my intention here to attempt even a cursory discussion of "color," an intricate subject; even its exact meaning, according to a number of authorities, is debatable. But pigment, technically, is defined as a dry substance which imparts color to bodies. It produces the sense of color by the absorption and reflection of selective parts of the incident light. Pigments are called colors in the form of paints and dyes. Paint, which is pigment carried in oil, albumen, or other adhesive, when applied to a surface is said to color it. Dyes are said to color materials by impregnating them with pigment. In biology, pigment is a genetic term for any organized substance whose presence in the tissues of animals and plants colors them.

Pigment is an integral and essential part of every photosensitive organism. Without it there can be no photoreception. Immediately after God said, "Let there be light," He must have created pigment. In some form or other it is present in every living normal

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eye, whether a single light-sensitive cell (ocellus), an "eye spot" or "pigment spot," which is one of the rudimentary sensory organs of some low animals, and the simplest thing that can be called an eye, or the highly developed mammalian eye of man. The phylogeny of eyes and the association of pigment with vision is a large subject and a fascinating one.* A thorough discussion of the origin, nature, and characteristics of animal pigment; its distribution, functions, and physiologic attributes in the visual sensation; the normal and pathologic variations of its distribution in the eye, and the clinical implications and inferences of these details, would, of course, fill many volumes. So, in order to keep within the bounds conformable to the occasion, I shall speak of a few points concerning the nature of pigment in general and discuss particularly some of the features—normal, anomalous, and pathologic—of pigment and pigmentation of the anterior parts of the eye which can be studied by ordinary clinical methods, especially slit lamp microscopy. I have chosen those points that, in my opinion, stand out and that merit discussion whether or not they are of material practical importance.

Edwards and Duntley [7] obtained the following pigments to account for the color of the skin: melanin; oxyhemoglobin; reduced hemoglobin; melanoid, which they were first to discover, and carotene, which they claimed was never before identified by spectrophotometry. These substances account for yellow, brown, and black. They quoted Hacker (1890) as the first to study the Tyndall effect. He decided that the color in blue feathers of birds is due to the presence of heavy masses of melanin behind a translucent, colorless layer of tissue. Edwards and Duntley's experiments led them to suggest that melanin in the skin will behave as though it were in solution; the greater the concentration the darker the shade. This we, as ophthalmologists, have for a long time known to be true of the coloration of the iris. Kuhne [17] described a brown pigment in the retina, fuscin, which is closely related to melanin; but whether it differs materially has not been definitely determined. Other pigments have been described; for instance, Flesch and Rothman [11] isolated a red pigment from the red hair of humans that is found nowhere else; this, they claimed, is different from brown-black melanin, and they suggested that it be called trichosiderin. The present knowledge of the nature and functions of such pigments as rhodopsin in their role in the photochemistry of vision has been aptly treated by Adler [16] and others.

Melanin is the term used to designate a natural, amorphous pigment matter or group of different, but related, pigments, the exact nature of which is not known. According to Lorincz,[9] it is a dyestuff of high molecular weight, insoluble in water and in most organic substances. Bloch, in 1917,† demonstrated that pigment cells contain a specific intracellular oxidase and that a substance which he called dopa was changed into melanin by this oxidase. When the substance is added to properly prepared epidermal cells of the skin or eye, granules of melanin are formed ("dopa reaction"). Bloch concluded that the colorless "mother substance" (melanogen), the same thing as or similar to dopa, when brought by the blood stream to a melanoblast, meets the "dopa-oxidase" and is turned into melanin. If there is no enzyme at all present, pigment cannot be formed and albinism results. But the dopa-oxidase concept has been vigorously challenged by a number of later investigators. Skin extracts were said to react not only with dopa but with other substances.[9] The exact process of the formation of natural melanin is still being seriously studied; there have been a number of postulates, but none has been universally accepted. As stated by Lorincz, melanin is found throughout the biological world, mainly to provide coloration. This pigmentary function has been elaborated into complex mechanisms for camouflage and sexual attraction, illustrated by a variety of striped, spotted, and seasonally changing coat patterns of animals, by the "ink" of squids, and by the remarkable

* Parsons,[3] Duke-Elder,[45] Vol. I, Chap. 1.

† Cited by Duke-Elder,[45] Vol. I, p. 373.

adaptive color changes possible in some reptiles, amphibians, and fishes. Some bottom-dwelling fish can accurately mimic not only color shade but also the pattern of their backgrounds. These changes are not for cosmetic effects—they follow certain definite rules for protective and functional purposes, dependent on environment and other factors.

It is generally believed that in all vertebrates melanin is formed primarily in specialized dendritic cells called "melanocytes." ‡ The relationship between hormonal factors and melanin formation has been widely studied both in lower animals and in man. Pituitary, thyroid, adrenal, and gonodial hormones have all been shown to influence melanin formation in living animals.

Formerly, the prevailing opinion, as stated by Fuchs,§ was that the two kinds of pigment found in the uvea are of different origin; that the one contained in the branched cells of the stroma, the stromal pigment, which consists of small, amorphous masses, is of mesodermal origin, and that the other, which consists of small rod shapes or crystals and fills the epithelial cells of the retinal pigment layer, is of ectodermal origin. Waardenburg [10] said that the stromal pigment is morphologically and chemically different from, and is formed much later than, ectodermal iris pigment. The trend toward the belief in a single origin for all pigment was probably started by Theobald [4] in 1937. She was convinced that the pigmented and nonpigmented cells of so-called sarcoma of the choroid are of neural origin, that they originate from the Schwann sheath cells of the nerves and traverse the choroid. Reese [43] pointed out that the Schwann cells do not normally produce pigment, but do so only when in pathologic states. Rawles [6] demonstrated to the satisfaction of most observers that all precursor pigment cells (melanoblasts) in amphibians, birds, and mice originate in the neural crest, although there is still some dispute with regard to the neural crest origin of the cells in man.[9] The time of development of the pigment of the eye is immediately after the development of the vascular system—end of the fourth week.‖ At this time small, brown retinal pigment granules have already made their appearance in the periphery of the cells in the equatorial region of the primary optic vesicle.¶

The movements of the pigment cells are controlled by the special chromatophore division of the nervous system, but the genetic factors which regulate melanin production, so as to account for the many normal variations in color, shade, and pattern of melanin pigmentation throughout the animal world, are largely not understood.[9] It is not known exactly how the chromatophores are distributed to the various parts of the body, or exactly when they reach those parts intended to be pigmented—the parts in which they are found later. These cells are distributed while they are still in their early melanoblast stage and as yet contain no pigment. As development proceeds and biochemical conditions become suitable, because of some stimulus or predetermined factor for melanin synthesis, these widely distributed "colorless" melanoblasts take on their characteristic differentiation; become melanocytes, that is, mature, melanin-producing, and melanin-containing cells, and are easily recognized histologically. Observed differences in melanocytes after the formation of pigment do not reflect corresponding differences in their original distribution. Probably many precursor pigment cells remain undifferentiated—free of melanin granules for long periods.[6] Melanin, therefore, is formed in the cytoplasm of melanocytes,

‡ At the close of the third conference on the Biology of Normal and Atypical Pigment Cell Growth,[5] because of confusion in terminology, it was decided to adopt the following uniform nomenclature:

Melanoblast: An embryonic cell potentially capable of producing melanin

Melanocyte: A mature melanin-producing and melanin-containing cell (previously this was called melanoblast)

Macrophage: A cell containing phagocytosed melanin

Melanophore: A pigment effector cell in lower animals

§ Fuchs,[48] pp. 29-30 and 36.

‖ Parsons,[46] Vol. 3, Pt. I, p. 903.

¶ Duke-Elder,[45] Vol. I, p. 326.

probably specialized nerve cells.[15] Stone [19] stated that under certain conditions melanocytes in salamanders can be developed into neural-type retinal cells.

In the lower vertebrates capable of rapid coloration changes, neural factors, usually visual impulses, influence pigmentation in a striking fashion. Blinding these animals generally causes paling of the skin. The efferent pathways act in part directly, by exerting an influence on the chromatophores, and in part indirectly, by activating such endocrine organs as the pituitary gland and the adrenals to produce hormones which regulate chromatophores.[9] It has been reported that molybdenum # and thallium * play a part in certain depigmentations. Excessive amounts of some trace metals in the skin—iron, silver, gold, bismuth, and arsenic—have been found to be factors in increased melanin formation.† Diet and vitamins are undoubtedly concerned with maintaining proper levels of melanin deposition, but the part they play is not exactly understood.

In general, the color of a tissue depends not only on the amount and the denseness of the deposition of the pigment cells but also on the pigment content of the cells, the evenness or unevenness of their disposition, their anatomic location, the quality of the surroundings, the degree of refractivity, transparency, or translucency of the optical media, the quality and intensity of the illumination, and the method of examination. Normal and pathologic deposits of melanin produce shades of black, varying from blue-black and jet-black to light slate-gray, in the fundus and sometimes in the sclera. But the natural intraocular pigment in the anterior segment of the globe, as seen by slit lamp microscopy, and also the natural pigmentation of the conjunctiva around the limbus, are never black, as the term melanin indicates; they are always a rich brown, golden-brown by direct illumination; the denser the deposit, the darker the shade. The color of a nevus of the iris is always brown; in the choroid a nevus, supposedly with the same pigment, is a shade of gray. Reese [8] stated that morphologically the pigments do differ, that the pigment seen in the pigment epithelium of the retina is black and composed of discrete rods, while the pigment in the chromoblasts of the uvea is light and appears as various-sized, amorphous, crystalline granules. The word "black" is sometimes used to denote the color or condition that is not black; for example, cataracta nigra, black cataract, is never black. Dark-brown irises are often called black; no normal human iris is black.

Pigment, of course, has no part in the sensation of color, such as iridescence of crystals in the cornea, aqueous, and lens, or iridescence at the surfaces of the crystalline lens by specular reflection and in complicated and senile disciform cataracts. The opacities of coronary cataracts, which are actually thin, colorless, sheet-like plaques, are seen as blue, greenish-blue, brown, black, or white. These effects are produced by the phenomena of light and depend on such factors as the thickness and translucency of the object, the transmission and reflection of the light, diffraction, interference, refraction, and the method of illumination—direct or retroillumination.

The play of colors seen in a sclerosing senile crystalline lens is due to the fact that the substance is no longer transparent to all of the visible light; that is, more and more of the light, from the blue toward the red end of the spectrum, is absorbed—the longer the wave length, the deeper the rays can penetrate the lens. The result is a coloration in the order of the spectrum from blue, in front, through green, yellow, and orange to red, progressing backward. This is not the same as the color of brown or mahogany cataracts. These are actually colored with pigment, as proved by a number of investigators.‡ However, there is no general agreement on the exact nature of this pigment or how it is formed. Bellows [24] suggested that because the composition of the coloring matter is unknown and variable, it should

Muir,[39] cited by Lorincz.[9]

* Gross and others,[40] cited by Lorincz.[9]

† Ormsby and Montgomery,[41] cited by Lorincz.[9]

‡ References 23-26.

be designated as a "melanoid" structure. Whether the same pigment has to do with the yellowish color of the senile lens is a question. The normal, faint yellowish glow of the corneal endothelium in situ is seen only in direct illumination along the line of specular reflection. In endothelial dystrophy and at the edges of a rupture of Descemet's membrane, the color is more conspicuous; it has more hue, and the tiny golden-brown tags of exfoliated endothelium may be mistaken for precipitated granules of uveal pigment. Sometimes, associated with dystrophy of the endothelium, there are numerous actual melanin deposits on the cornea, which are not always easy to differentiate from the distintegrated cells; but these deposits are not an essential part of the disease, because, as it progresses, the pigment granules become fewer and fewer, and eventually, in the final stage—guttate cornea—the tags, pigment, and yellowish color will have entirely disappeared. Another example of the effect of light on the resultant color sensation is seen when the iris appears to be of a bright blue. This takes place when the retinal pigment is intact and the stroma is entirely free of pigment. By slit lamp microscopy the apparently rich-blue iris is composed of colorless trabeculae, colorless connective tissue, and the dark-brown pigment epithelium. Here, the light, mostly the short waves, is diffracted and scattered by the translucent trabeculae just in front of the normal brown background. This is the phenomenon already mentioned—Tyndall reaction—which is responsible for the blue color of feathers, the color of veins under the skin, ecchymoses, tattoos, and the blue sky.

Sonderman [18] stated that the pigmentation of the stroma of the iris is based on the rate of obliteration of purely embryonic vessels and that the survival time of erythroblasts in the circulating blood is a factor that determines the intensity of mesodermal pigment formation. This explanation seems to be more applicable to the pigmentation of the retinal pigment layer than to the stroma. The pigmentation of the retinal layer of the iris follows a fixed rule—it is pretty solidly pigmented at birth. The cylindric cells of the pigment epithelium, as described by Salzmann,§ are so densely filled with dark, round, gross pigment granules that neither cell borders nor nuclei are visible microscopically. Only by studying bleached preparations can individual cells, as elements, be made out. These pigment epithelial cells of the iris form a smooth, dark-brown membrane that is normally impervious to light. This opaque structure has a definite function in ocular imagery. With its opening, the pupil, it is the actual stop and stop-aperture of the optical system of the eye. It also reduces to almost zero the reflections inside the eye, those of the second order, the rays called "nuisible," "harmful," by Tscherning,[44] which could spoil the retinal image.

Around the pupillary border the pigment epithelium forms what has been called a seam, ruffle, or ruff. This is the transition point, the limit of the optic vesicle, the place where the outer leaf turns back to form two layers, in the neighborhood of the pupillary zone of the iris, and insures doubly against the entrance of extraneous light in the vicinity of the pupil. In this area one layer is adherent to the undersurface of the iris, and the other moves freely over it to some extent. It projects toward the front around the rim of the pupil to form the physiologic ectropion of the pigment epithelium.|| Depigmentation of the retinal epithelium around the pupillary border and zone nearby is seen so frequently in old people that it must be considered a normal physiologic process in senility. This condition has been said to be a consequence of local arteriosclerosis and faulty circulation, since the nutrition here is dependent upon the terminal fringe of iris blood vessels [30] (Friedenwald and others¶). Except in elderly persons, therefore, depigmentation of the retinal epithelium is a pathologic sign. Since depigmentation takes place eventually in nearly every person, and since there is no sharp time for the inauguration of senility,

§ Salzmann,[47] p. 114.

|| Salzmann,[47] p. 144.

¶ Friedenwald and others,[51] p. 45.

it is sometimes not easy to decide whether the depigmentation is due to disease or not; it is up to the examiner to determine whether the degree seen is conformable to the age of the patient, but widespread loss of retinal pigment is pathologic at any age. The ruff in the aged will be wider than that in a young person because of the normal miosis of old age. Any material absence of retinal pigment in the pupillary zone that involves the border results, of course, in loss of the ruff and lessens the curvature of the pupil. The straightened portion here will be less active during contraction and dilatation than the rest of the pupil. In many instances there will be segmented depigmentation, and sometimes no ruff at all. The depleted areas around the edge of the pupil will be replaced by a more or less pigment-free, translucent hyaline membrane. Loss of retinal pigment can be detected easily by transillumination or retroillumination because, as already stated, intact normal retinal epithelium does not transmit light.

The width and shape of the retinal pigment layer which goes to form the physiologic ectropion vary considerably. Sometimes the variations are striking and may be familial.[20] In rare instances the layer is even doubled. The ruff may be very thin; it may not even be seen in places. Vogt # explained that the eversion of the border of the iris, lifting it up from the surface of the lens, seen often in the miosis of elderly people, is the result of senile rigidity of the stroma. The use of strong miotics will always increase the width of the normal ruff, exaggerate the ectropion uveal, and sometimes cause the appearance of globular and cyst-like protuberances. Such terms as "pilocarpine cyst" * and "intraepithelial cysts" [22] have been used to designate these conditions. They resemble in all respects the types so often described [20] as congenital ectropion, ruffles, folds, cyst-like globules, congenital cysts of the uvea, flocculi, knobs, excrescences, and by other names for a variety of nonpathologic anomalous ruffs. Possibly they are pouches or sacs formed between the two layers of the pigment epithelium, local dilatations of persisting portions of the marginal sinus. They certainly can be emptied and refilled. Ordinary degrees of these are not uncommon. The cases illustrated by Abraham [22] are extreme examples, and it is remarkable that they are entirely due, as he claims, to the prolonged use of strong miotics. Any benign and congenital anomaly of the retinal pigment border of the iris characteristically increases in size with miosis. It is one of the diagnostic means of determining the benignity of these protuberances that they are exaggerated on contraction of the pupil and are diminished in size—may even disappear entirely—on mydriasis. One reason for this is that the outer border of the ruff is attached to the collarette by fine, inelastic strands.[3] On the other hand, a new or pathologic growth at the border or on the posterior surface of the iris behind the border will be further exposed during dilatation, and be hidden, more or less, even entirely, by contraction of the pupil. A pathologic ectropion, for example, in the case of essential atrophy, in which the pigment epithelium lies out on the face of the iris like a bib, would either be unchanged or become larger if mydriasis were possible. Slit lamp microscopy of the iris is never complete unless it is done under both miosis and mydriasis.

While the normal pigmentation of the ectodermal portion is practically the same in all persons, the order of the pigmentation of the mesodermal portion of the iris seems to follow a physiologic preordained course for each person. It resembles that of the hair—the deposition increases after birth, up through childhood and adolescence and into adulthood. After this, depigmentation takes place, and the amount of pigment is lessened progressively as a manifestation of senility. Even in those instances in which there is complete absence of stromal pigment of the iris in an infant, eventually some pigment will surely be seen as the child grows older. Pure blue irises, as is well

Vogt,[3] p. 116.

* Vogt,[30] p. 832. Berliner.[21]

known, are normal only in white infants and in very young blond children. The findings of Rawles,[6] already noted, that many precursor pigment cells remain free of melanin granules for long periods of time may well be the explanation for the course of the pigmentation of the iris stroma.

As stated before, when the mesodermal parts of the iris are entirely free of pigment, the eyes will be blue by ordinary observation. When the pigment is thinly and superficially distributed, the iris appears to be a very light yellow under the slit lamp, but grossly it is a bluish gray; and so eyes are said to be yellowish, greenish, piebald, light brown, or dark brown, depending on the richness and pattern of the deposit of pigment, and the other conditions already mentioned. The architecture is, of course, most outstanding in those irises that are scantily pigmented, not only because it is more easily seen, but also, as is usual in these eyes, because of the consequent thinness of the trabeculae and the connective tissue. In these eyes the pigment is found almost exclusively in the anterior border layer. As the pigment is increased in amount and extent, more and more of it is found throughout the stroma, until the trabeculae are entirely surrounded with pigment; and when it is densest, no crypts are seen, the structure of the iris is entirely obscured, and the surface is a smooth, mossy, rich brown—the eye they call black. These irises are the thickest, and are generally more sluggish than those not so heavily pigmented. It seems likely that the large amount of pigment has a tendency to impede the activity to some extent. Such irises as these are not common even in the darkest people; it is seldom that at least a few crypts are not found, with, deep down in them, some colorless connective tissue. Usually the iris is more pigmented near the pupillary border and around the collarette, because in these places the anterior border layer is thickest. It is thinnest on the floor of a contraction furrow; on this account, the furrows can never be obliterated (Salzmann †). It is hardly logical, as proposed by Mawas,[12] that the lessened deposit of pigment in the trough of the furrow is the result of the movements of the iris during dilatation and contraction; rather, it is a normal thinning here to facilitate the movements of the iris.

Isolated collections of pigment cells (benign melanomas, nevi, freckles) are often seen in any type of iris. Around the pupillary zone near the border and in the region of the sphincter, small dark spots, accumulations of very dark pigment cells, may be found. These are the clump cells of Koganei, which are known to be displaced from the ectodermal layers of the posterior surface.‡ They are seen in irises regardless of the degree of mesodermal pigmentation.

It is remarkable how the changes in color of the iris throughout life, that is, the amount of melanin, are approximately the same in both eyes. In the relatively uncommon exception to this, when one iris is darker in shade than the other, or even entirely different—one a light gray and the other a dark brown—all possibility of a pathologic disturbance must be carefully ruled out before it is diagnosed as a benign developmental anomaly. Extremely low-grade, chronic uveitis is not uncommon. Even the typical or atypical Fuchs' heterochromic cyclitis[35] is commoner than has generally been recognized in this country, as pointed out in a recent article by Kimura, Hogan, and Thygeson.[36] The classic characteristics of Fuchs' syndrome are well known; but the disease runs such a quiet course over so many years that the clinical picture, especially since there are practically no subjective symptoms for a long time, is such that often it is difficult in the early stages to decide whether the condition seen is quietly pathologically active, the sequence of an arrested, previously active process, or a nonpathologic anomaly. Of course, if the signs correspond in every respect to the definition of Fuchs' syndrome, the diagnosis is easy; but this is seldom the case. Kimura and associates, in their paper, call attention to the importance of diagnos-

† Salzmann,[47] p. 132.

‡ Salzmann,[47] p. 136.

ing Fuchs' syndrome in its incipience, when both objective and subjective signs are vague, and in those extremely rare instances in which there is no heterochromia or when both eyes are involved. It should be remembered that, while usually the diseased eye becomes lighter on loss of mesodermal pigment, it happens on rare occasions that in blue or light-gray irises the disease can, by overexposing the brown pigment layer, cause the sick eye to appear darker than the healthy one. It is difficult at times to determine whether the lessened amount of stromal pigment in the ciliary zone is normal or is due to absorption. In Fuchs' syndrome the pigment epithelium undergoes atrophy at the same time as, or even before, the stroma is affected; the condition differs, therefore, from essential atrophy, in which the pigment epithelium usually remains apparently intact until after the stromal atrophy is well advanced.

In the skin of persons of the light races the manufacture of pigment by the melanocytes is stimulated by the sun, resulting in tanning and freckles. Afterward, when it is no longer or is less exposed, the skin becomes pale again. The pigmentation of the skin of the Negro differs from this; here it is similar to that of the retinal pigment layer of the iris—it is practically constant from birth. Pillat [14] said that, biologically speaking, the main purpose of pigment is to serve as protection against light; that the important cells of the epithelium are the basal cells, which have the function of multiplying and delivering new cells to the more superficial layers. A meshwork is formed of brown pigment, which absorbs light and keeps it from hurting the basal cells. This effect, by exposure to sunlight, occurs in the conjunctiva, but not in the iris, although the chromocytes, as far as is known, are the same. The reason might be due to the absorption of ultraviolet light by the cornea and aqueous.

It is possible, however, that Stähli's,[28] or Hudson's,[27] line and the pigmentation of old scars of the cornea are defense reactions against sunlight. This hypothesis may be far-fetched, but it is as good as any other that has been proposed. The pigment in Hudson's line lies in breaks in Bowman's membrane, according to Grüninger.[13] The pigment, yellow or light-brown and extremely fine, can be seen immediately under the epithelium in Bowman's zone. It is found quite often in elderly people without evident cause, and is said to result from the migration of cells of the pigmented epithelium of the limbus over the surface of the cornea (Friedenwald and associates §). This may be true, but the pigment is never seen on the way to its destination. Duke-Elder ‖ stated that Hudson's line occurs commonly in eyes of people who work with hydrogen sulfide, hydroquinone, or quinacrine (Atabrine). Fleischer's ring, around the base of the cone in keratoconus, resembles Hudson's line. This pigmentation is also in Bowman's zone and might well lie in a weakness or break in Bowman's membrane at the base of the cone, just at the edge of the diseased portions of the cornea. The pigmentation in old scars of the cornea is similar in appearance to that of Hudson's line and Fleischer's ring, and it, too, lies directly under the epithelium or in Bowman's zone, extending sometimes into the stroma. The pigment in these conditions appears and has been said to be of hematogenous origin, but it seems to come from nowhere; blood vessels are seldom seen anywhere near the deposit.

It might well be that pigment is involved somehow with the healing process. It is possible that the pigmentation seen in so many pathologic conditions—tapetoretinal degeneration, senile macular degeneration, retinal detachment, trauma, chorioretinitis, old corneal precipitates, and other products of inflammation—is a manifestation, though probably often futile, of a defense mechanism. In many instances, however, it is hard to tell whether the pigment changes which are seen are due to proliferation of cells, an increased number of cells, or to the spilling of pigment from sick or weak cells, with the probability that some of the spilled pig-

§ Friedenwald, and others,[61] pp. 220 and 236.
‖ Duke-Elder,[45] Vol. VI, p. 6610.

ment is phagocytosed by endothelial cells (Friedenwald and associates ¶).

The migratory action of pigment is not well understood. The ability of pigment cells to go from place to place can be explained by the capabilities and characteristics with which living cells are endowed, but the seemingly methodical movements of the dead pigment granules is inexplicable. They seem to have an affinity for certain parts and, in their migration toward their destination, the capacity for passing through membranes considered not easily penetrable, for example, the capsule of the lens and Descemet's membrane. Parsons # said that the lens capsule was permeable to fluids and to iron-containing pigment in the form of brown granules. Friedenwald [1] showed that the lens capsule is permeable to a number of dyes and many other substances—electrolytes, true solutes in water, and small and medium-sized colloid substances. He does not mention natural, organic pigments. Gifford and associates [87] found the normal lens capsule permeable to water, electrolytes, and substances such as sodium salicylate and fluorescein, with no mention of natural pigments.

Commonly an aggregation of fine, dust-like, reddish-brown pigment granules occurs on the anterior capsule of the lens. This is not the same as the accumulations of cells or coarse pigment granules in clumps, or star figures, sometimes the remains of pupillary membranes or of previous inflammation or degeneration, so frequently seen. Neither is it the same as the condition Bellows [84] described, which is probably a leaking of uveal pigment from the retinal epithelium in lines radiating from behind the iris, toward the center of the pupil. The pigment in all of the latter cases is plastered on the capsule and remains there, often unchanged for years. The aggregation I mean does not resemble, and has no relation to or association with, the ordinary uveal pigmentation of the iris or of the back of the cornea. It is composed of exceedingly tiny grains, apparently all the same size, and at first are not all brown; some are grayish in color. After a time they penetrate the capsule, enter the lens, spread out, and wander deep into the adult nucleus. Eventually they disappear in the lens substance. It occurs after adulthood, mostly in women with otherwise apparently healthy eyes. These might correspond to the brown granules of iron-containing pigment, which Parsons said were found to have penetrated an intact lens capsule; and from their appearance they could well be derived from blood, but from where, it is hard to say.

In blood staining of the cornea from hyphema the pigment granules first adhere to the surface of the cornea, and then penetrate the endothelium and Descemet's membrane, to begin their characteristic passage through the stroma. They take on a certain pattern, too; provided sufficient blood is in contact with the cornea, and for a long enough time, they congregate in a circular formation. The disk-like figure is densest in the center and fades out toward the periphery. Usually there is a lucid interval around the limbus. The picture is very much like a lens dislocated into the anterior chamber. It has been stated (Duke-Elder *) that, as a rule, to produce this effect the anterior chamber must be filled with blood, that it is a moot point whether the pigment granules are absorbed through a damaged endothelium, and that (Parsons †) it is possible that the tension is always raised, at least in the early stages. In my experience none of these conditions is necessary. I have seen it occur when the anterior chamber was not much more than half full, and the upper border of the pigmentation well above the level of the hyphema, and therefore not in direct contact with the blood, with an intact endothelium and Descemet's membrane, and with no increase in intraocular pressure. The pigment, which at first is composed of closely packed granules of a dark reddish-brown, with a slight greenish aura, in time becomes lighter in color as it comes forward and

¶ Friedenwald and others,[51] p. 45.
# Parsons,[46] Vol. II, p. 42.

* Duke-Elder,[45] Vol. VI, p. 5768.
† Parsons,[46] Vol. I, p. 249.

thins out from the periphery in—the last of it will be seen near the center. Finally, after many months, it looks as if the pigment leaves the cornea through its anterior surface. In blood staining, the result of subconjunctival hemorrhage, the pigment granules may be seen more frequently posteriorly in the cornea, and gradually to migrate toward the center and forward. These processes are similar to that described by Lorincz [9] for the excretion of melanin granules by the skin, that is, upward through the epidermis, with ultimate loss from the surface, along with the physiologic shedding of the horny layer.

It is strange that, although the blood in hyphema is in contact with the lens capsule, as well as with the cornea, there is no blood staining of the lens—strange because we have just seen that fine granules, probably blood pigment, can easily adhere to the lens capsule and eventually penetrate it. It is strange, too, that free blood in the cornea remains the same, bright red, and in the same spot for years.

Frequently we see, because of trauma, degeneration, or inflammation, or for no apparent reason, both the mesodermal and the ectodermal part of the iris become depleted of pigment and/or pigment cells. It is well known that in diabetic patients in whom, as part of the disease, the ectodermal cells are diseased and swollen, occasionally mere contact of the iris with a sharp instrument is enough to cause so many cells to discharge their pigment that the whole aqueous becomes inky. A disturbance of pigment can result from any insult to the iris or ciliary body. After an iridectomy the pillars of the coloboma always show pigment absorption—atrophy, more or less, of both the stroma and the retinal epithelium, with migration of pigment. Some atrophy of both the mesodermal and the ectodermal part of the iris and migration of pigment take place after every intraocular operation.

A posterior synechia starts with a parade of pigment onto the lens from the margin, or from behind the margin, of the pupil. This is before there is any attachment—the cement substance which binds the iris to the lens comes later. The exudation which produces a posterior synechia at the pupillary border comes mostly from the mesodermal portion of the iris. In adhesions between the lens and the posterior surface of the iris, the retinal pigment epithelium adheres more firmly to the lens than it normally does to the stroma and usually pulls away later in sheets. It leaves a hole in the retinal pigment epithelium which is easily seen by retroillumination.

As part of the physiologic process of senility, pigmentary changes occur, of course, in the eye, as well as in other places in the body; they may be seen in the eyes of everyone over 50 years of age. Depigmentation of both the ectodermal and the mesodermal portions of the iris begins with senility and progresses steadily throughout life. Pigment deposits in the anterior chamber are seen so frequently in apparently healthy young people that they must be attributed to some factor or factors other than senility. Evidently uveal pigment is liberated often on the slightest provocation. It is possible that in some instances what is seen is the product of mild transient uveal inflammation that became pigmented later, just as in the larger, lardaceous precipitates in severe uveitis, which, after the inflammation subsides, become dryer, thinner, more sharply defined, crenated and eventually, in some unexplainable way, pigmented until, finally, they appear as nothing but fine brown granules. Incidentally the keratic precipitates in Fuchs' heterochromic cyclitis do not become pigmented; they remain a dirty white. This, together with the white vitreous opacities and the pigmentless exudates on the iris, lends support to the theory put forth by Duke-Elder ‡ that in Fuchs' syndrome the pigment-producing cells, for some reason, fail to develop into properly functioning chromocytes. Whatever the exciting agent, complete cells or their melanin contents can easily be made to come away from the iris or ciliary body.

‡ Duke-Elder,[48] Vol. II, p. 2362.

Eventually, in every old case of chronic uveitis or glaucoma the retinal epithelium may be seen by retroillumination to be thin, friable, and depigmented completely in places —holes—or evenly thinned over its entire extent, like a gauze or gossamer. It is difficult at times, when there is a meager amount of pigment in the iris stroma of each eye, to determine whether the amount is normal or whether some of it has been lost by absorption. As has already been said, since one cannot tell exactly when senility begins, it is often a question whether the case under observation is a manifestation of premature senility, endocrine dysfunction, dystrophy, trauma, degeneration, or inflammation.

As a result of disintegration, the uveal pigment cells or the liberated melanin granules enter the anterior chamber and are conveyed by the flow of the aqueous until they find a lodging place. We see pigment cells or granules as fine peppering accumulations in flecks, heaps, and clumps, spread out all over in profusion or crowded on the surface or in the stroma of the iris, on the lens, capsular remains, exposed vitreous, hyaloid, and/or the cornea. Actually, of course, the outlines of individual cells cannot be made out by ordinary slit lamp microscopy. I cannot agree with Kraupa,[30] and a good many others more recent, in the belief that fine granules of pigment do not cling to an intact corneal endothelium. Support for this is not borne out in my experience. If it were true, there would have to be a roughening or denudation of corneal endothelium in practically every adult. It is reasonable to suppose that adherence of precipitates is favored by a diseased endothelium, but there is no doubt that they will adhere to a perfectly smooth surface. Pigment in the anterior chamber probably sticks to the first place it strikes, and, naturally, the amount deposited on the cornea varies.

In 1899 Krukenberg[31] described the spindle-shaped pigment deposit on the posterior surface of the cornea, which he called congenital melanosis. He and, for a long time, many others believed it to be congenital, a persistent remains of the pupillary membrane, and due to some prenatal fault. It was thought for many years to be a rare condition, almost always occurring in women with brown irises and with associated myopia, a congenital anomaly, even though it had never been seen in a child.

Edgerton,[32] in 1930, in his exhaustive discussion and review of the literature up to that time, reported what he believed to be the 36th case—in a man, and with hypermetropia. He believed the lesion to be of congenital origin. As slit lamp microscopy became more generally used, opinions regarding its nature and origin gradually changed. Also, it was more frequently seen; by 1941 Evans, Odom, and Wenaas[33] had collected 202 cases. They did not believe it is congenital, and they stated that by that time Edgerton agreed with them. After many years of routine slit lamp examination of nearly every patient, I am convinced that so-called Krukenberg's spindle is not an entity. Its only significance is that if pigment granules are carried by the convection currents of the aqueous, the deposition will naturally assume a spindle-shaped formation in most instances. In the case of only a few precipitates they will usually be found in this location. Practically the same mechanism takes place with every type of exudate. In acute or subacute uveitis the products of the inflammation are generally more numerous over a roughly fusiform area, mostly in the lower quadrant. This is due to gravity and to the downward flow of the aqueous in the anterior part of the anterior chamber. Usually, when there is much pigment scattered over the posterior surface of the cornea, the population is greatest in an area corresponding to a vertical spindle and, when sufficiently dense, may be seen by oblique illumination with a magnifying glass; but in almost every case some granules can be found all over the posterior surface of the cornea. Pigment deposited in spindle formation is not rare; in fact, it is commonly seen by slit lamp microscopy. In most patients who are carefully checked from time to time a definite arrangement of deposition will be seen as pigment is increasingly deposited.

At times I have seen the fusiform arrangement take place within a year or two. But to come across a case of pigment granules on the cornea so neatly placed that all granules are contained in a sharply defined spindle, according to the classic text-book description, and as depicted in drawings supposed to illustrate this phenomenon, is indeed rare. I cannot believe anyone has ever seen anything that resembles, even remotely, some of these pictures. Of course, we know now that the condition is certainly not congenital; that it occurs in eyes regardless of the color of the iris; that the denser, central portion may take on forms not exactly spindle-shaped and not vertical, even horizontal ones having been reported. The cause is surely the same as that of all uveal depigmentation and migration. How simple myopia can be considered an etiologic factor is hard to understand—it is found in any type of refraction.

In order to provide some concrete data, we took haphazard 75 records of cases that I should include in this category; all were bilateral; all had some degree of disintegration of iris pigment. In these conditions, which are no doubt the result of low-grade uveal degeneration or inflammation, an association of endothelial dystrophy is to be expected—it was found in 17 patients, 12 women and 5 men. There were 45 patients with brown and 30 with gray irises. Their ages when the patients were first seen varied from 17 to 80, most of them (42) being in the fourth, fifth, and sixth decades; hypermetropia was found in 38 persons, myopia in 33, and mixed astigmatism in 4. It occurred in 51 women and 24 men. The large proportion of women to men conforms to the predominance of endothelial dystrophy in women over men, as found by Goar.[38] It is obvious that there must be many different causes for the various types of these affections, but the prominent circumstance that conditions involving uveal pigmentary disturbances are exaggerated, and invariably much more prevalent in women than in men, is reasonable evidence that some dyscrasia peculiar to women is a likely and important etiologic factor in many types of uveal disease.

A discourse of this kind must needs come to a somewhat abrupt end, and so I shall conclude by saying that, although there has been a great amount of research done on natural pigment, it is obvious, from a perusal of the literature, that, while the amount of knowledge brought to light is tremendous, there are still many defects, and consequently much speculation and controversy; there is no universally accepted concept of any phase of the subject—chemistry, origin, formation, distribution, nature, or characteristics—in either health or disease. Compared with the amount of research in general ophthalmology, the topics of ocular pigment and pigmentation have been slighted. They offer a wide field for investigation—investigation that ought to be done by ophthalmologists.

1930 Chestnut St. (3).

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On the Precise Objective Determination of Eye Movements

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In the usual course of a prism-vergence test, the eyes are slowly forced to converge (or diverge) until the subject reports that he sees the test object double. Then the prismatic power is slowly decreased, and, at a certain point, fusion of the double images is suddenly regained. Just at this moment when recovery of fusion takes place, the two double images must have attained a certain critical separation, which is capable of initiating fusional movements of the eyes to overcome the diplopia. If, just at the moment of recovery, one of the double images falls in the fovea of one eye, the other image will necessarily fall extrafoveally on the retina of the other eye at a certain angle, an angle of disparity, which is one dimension of the so-called perimacular fusional area.[1] It has been generally assumed that in the prism-vergence tests, as soon as the images of a test target are seen double, the eyes immediately revert to the heterophoria (the fusion-free) position. Hence the recovery point in the test would be definitely related to the phoria position of the eyes by this relatively small convergence angle.

There is ample evidence, however, that the unusual tonicity of the extraocular muscles caused by the gradual increase in forced convergence (or divergence) is maintained to a certain degree for a considerable time after the stress is eliminated.[2] Hence for most subjects the eyes could not be expected to revert at once to the heterophoria position after the point of doubling. The recovery point would not necessarily be related to the original heterophoria, and estimates of the perimacular fusional area so obtained would not be accurate.

Since the concept of perimacular fusional areas is important for our understanding of the fusional processes in binocular vision, it is desirable to obtain more data concerning it. To obtain those data, however, it is necessary to know where the eyes are pointing, as well as to know the convergence angle of the test targets at the moment of recovery of fusion. For peripherally located test targets the technique of using vernier (nonius) lines is a practical one.[3] This method, however, cannot be used to obtain information when the target images are to be fused foveally. Consequently a photographic method of recording the positions of the eyes by means of the corneal reflex was used. On the same film record a trace showing the convergence angle of the test targets was impressed. Thus, throughout the prism-vergence cycle, the difference in the angle of convergence of the eyes and the angle of convergence of the images of the target could be known at all times.

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The broad body of data on which this paper was based constituted material from which Drs. Tani and Weaver produced theses submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Ophthalmology.

This method proved not only feasible * but useful, although at the outset it was found that, following a prism-vergence cycle of "break" and "recovery," the eyes did not return to the original "zero" position. This error in some instances amounts to as much as 3 △. It was first assumed that this discrepancy was an artifact of the apparatus, and that only a corrected calibration curve was necessary to determine actual convergence positions of the eyes from the photographic records. A more extensive study showed, however, that the discrepancy in the return of the eyes to the base line was not an artifact of the apparatus, but a physiologic phenomenon taking place as the tonic states of the muscles were modified by the sustained forced convergence.

The purpose of this paper is to describe the apparatus used for the objective determination of the eye movements and to analyze the discrepancy found in terms of properties of the eye movements under conditions of stress.†

APPARATUS AND METHOD

A modified 35 mm. ophthalmograph camera, for photographing the catoptric images reflected from the corneas of the two eyes, was mounted on a large haploscope supported on a rigid steel table (Fig. 1). By means of a suitable headrest and biting board, both eyes of the subject could accurately be placed directly above the pivot points of the arms of the haploscope which supported the targets. The supports for the two haploscope mirrors, mounted on the arms before the eyes, were so offset that they did not interfere with the photographing of the corneal reflexes.

Two electric lamps were mounted in suitable housings on each side of the camera to serve as light sources for the corneal reflexes. Since those corneal-reflex images lay about 4 mm. in front of the centers of rotation of the eyes, their apparent displacement photographed by the camera on continuously moving motion-picture film was a measure of the change in rotations of the eyes. Calculation shows that with this experimental arrangement for rotations of the eyes nasally up to 20 arc degrees, the angular displacement of the image photographed by the camera is accurately proportional to the angle of rotation.

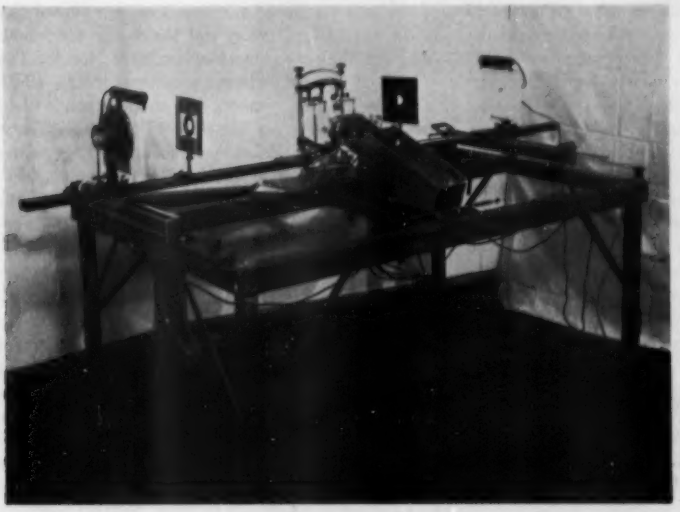

Fig. 1.—Apparatus showing ophthalmograph camera mounted on haploscope for photographing eye movements during prism-vergence tests.

The patterns used for fixation and for the fusion stimuli were drawn on large white cardboard and were attached to targets, each with its own source of illumination, mounted on the arms of the haploscope. The distance of these targets could be changed for any desired distance from the eyes. Apertures of unlike shape and size were also placed on the arms about halfway between targets and eyes in order to eliminate any other similar contours save the pattern on the targets.

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Divergent and convergent movements of the arms of the haploscope, and therefore of the targets, were controlled by means of a handwheel which activated a rack-and-pinion arrangement connected to a continuous cable, which, in turn, was connected to both arms, so that any movement of the wheel resulted in equal and synchronous movement of the two arms with no backlash. Thus, convergent and divergent displacements of the targets were divided equally between the two arms. A meter stick was affixed under the path of movement of one arm and at a right angle to the arm itself when set corresponding to the primary position of the eye. The convergence position of the arm could then be read on the scale in centimeters. This reading, in turn, would be proportional to prism diopters of convergence.

The ophthalmograph camera was so modified that it recorded simultaneously the positions of the eyes and the corresponding convergent or divergent position of the two targets on the haploscope. To provide for the latter recording, a small optical unit was mounted within the camera housing to project an image of a point of light on the film at the same level as the record of the images from the corneal reflexes. This projector was mounted on a vertical spindle which rotated through a small angle corresponding to the convergent movement of the arms of the haploscope. This spindle was activated by a lever in contact with a cam, which was, in turn, rotated through an assembly of gears, attached to the rotor of a Selsen generator. The companion generator was activated by the handwheel which controlled the convergence movements of the two arms of the haploscope. Thus the position of the image on the film was closely linked electrically to the convergence of the haploscope arms. The light from the projector was interrupted for a fraction of a second at intervals of one second in order to provide a record of the passage of time involved.

The subject sat on a stool directly in front of and facing the camera. The head was adjusted to the instrument and held steady by means of a headrest with four adjustable forehead cushions and with a rigid biting board. The heterophoria position of the eyes for a given object distance was initially established by using a spot on the left target and a vertical line on the right target. The convergence of the arms of the haploscope was then adjusted so that the spot and the line appeared superposed. This convergence position of the targets corresponded to the lateral phoria position of the eyes.

For the fusion-convergence tests, identical long, narrow vertical lines drawn on heavy cardboard were used as the targets. The arms of the haploscope were first set for a convergence corresponding to the dioptric distance of the targets mounted on the arms from the eyes. The two images of the two lines could then be fused easily by the patient and would be seen as a single vertical line. At first, when the convergence was set normally, the corneal reflex images were focused as usual in the ophthalmograph. However, greater care was taken to focus the images as accurately as possible and to align them on the centering lines of the ground glass. If the haploscope arms with the illuminated targets were then converged, the eyes were likewise forced to converge if fusion was to be maintained. On the other hand, divergence of the arms resulted in a forced divergence of the eyes.

On the developed film there therefore were three traces, corresponding to the continuous movement of the two corneal reflexes and to the convergence of the targets. From the time-target trace, the actual convergence of the haploscope targets could be determined. Figure 2 illustrates the traces on a strip of the film chosen at random. The interrupted line is the time-target trace, and the fairly continuous lines are the two corneal-reflex traces for the two eyes. The distance between these two traces, which is the measure of convergence of the eyes, will be called the "intertrace distance." The uniform inner edges of the sprocket perforations of the film were used as the base line from which the displacement of the time-target convergence trace on the film was measured. This displacement is the measure of the convergence of the targets on the haploscope. Tests showed that this method of measurement was accurate to within an estimated 0.5 △.

For a given run, the data to be obtained were the distance of the time-target trace from the edge of the sprocket holes and the intertrace separation at various successive times from the beginning of the run. To facilitate these measurements, the film was placed in an American Optical Company microfilm reader, which provided a projected image of the film on the easel magnified 15 times. The desired measurements could then be made with an ordinary millimeter scale. Actually, the film record was "telescoped" by passing the film slowly through the projector and plotting the trace positions for the end of each succeeding second on closely spaced vertical lines on chart paper on the easel of the reader. From this shortened record the desired measurements were obtained.

A primary calibration related the distance of the time-target trace from the edge of the film, in millimeters, to the actual convergence of the arms of the haploscope, in prism diopters. A separate run, without a subject, was necessary for this. A calibration graph was then prepared from these data.

After the patient's head was properly adjusted to the apparatus, he was told to maintain absolute attention to the line targets. The procedure was then as follows: First, with the targets set for the normal, or phoria, position, the film was run for a period of 40 to 80 seconds to locate the base line

for the traces of the target convergence and for the convergence of the eyes. After this phase, the arms of the haploscope were caused to converge at a fairly uniform rate, which procedure, in turn, forced an increasing convergence of the eyes. This increase in convergence was continued until diplopia occurred. By watching the eyes of the subject, the operator could observe when this happened. The convergence of the targets was, however, continued even well beyond that point in order to insure definite separation of the target images. The direction of movement of the targets was then reversed in order to decrease their convergence gradually. At some point recovery of fusion occurred, but the decrease in target convergence was continued to the normal, or phoria, position. The film was allowed to run at this position for about 40 seconds. The divergence cycle was then started, during which the targets were moved to cause a relative divergence of the eyes.

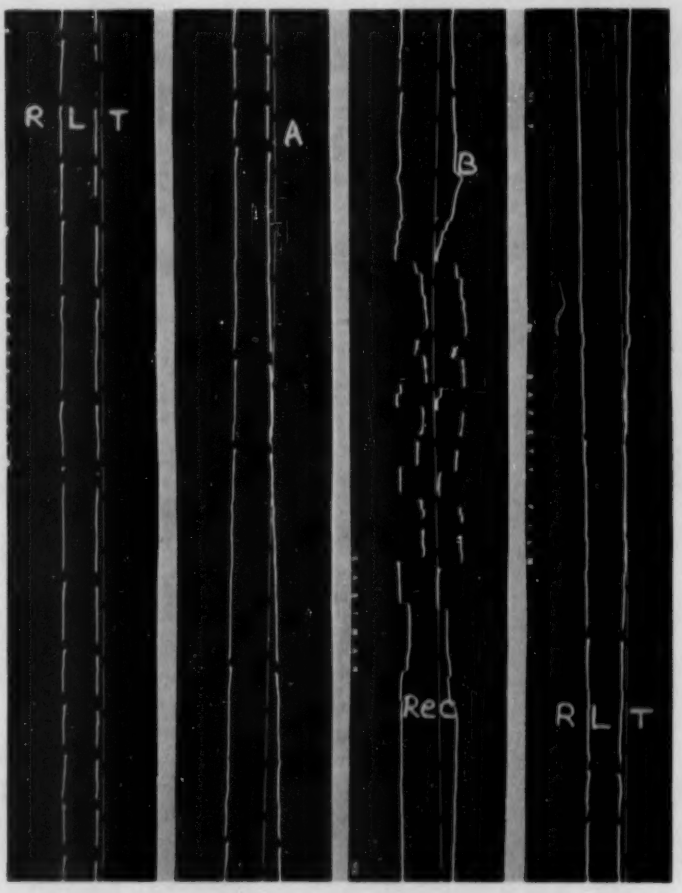

Fig. 2.—Photographic prints of portion of a film for forced convergence. *R* and *L* are the corneal-reflex traces for right and left eye, respectively. The interrupted line is the target-convergence trace. Point *A* is beginning of forced convergence; Point *B* is point where fusion is broken, and *Rec* is point of recovery of fusion.

More than 20 different subjects were used in this study, several films being made for each subject. One subject was studied intensively in a series including more than 24 film strips. These subjects were young men and women, all with normal binocular vision. None wore spectacles during the tests.

The results from a given cycle of forced vergence were shown on a single graph, obtained by plotting the time, in seconds, as the abscissa, and both the convergence of the target arms and the corresponding convergence of the eyes (both in millimeters), as the ordinate. Figure 3 illustrates a typical graph obtained in this way. The interrupted lines describe the convergence of the eyes, and the solid lines describe convergence of the targets. Data points plotted positive on the ordinate indicate a convergence, and those plotted negative indicate divergence.

The calibration of the convergence of the eyes from the traces found on the film can be obtained

directly from the graphic representation of the measurements, as shown in Figure 4. Clearly, in that portion of the graph where the forced convergence increases, the eyes, to keep their images fused, must have maintained fixation on the target lines. Hence the convergence of the eyes must be the same as the convergence of the arms of the haploscope in this portion of the data. Thus, the relationship between the intertrace distance and the equivalent convergence, in prism diopters (or meter angles), is found directly.

OBSERVATIONS

The first discrepancy encountered in trying to analyze the film records was that the calibration curve used for that portion of the graph showing increasing forced convergence did not correspond to that of the decreasing convergence after passing through the diplopia and recovery points. In the typical graph in Figure 4 the raw data obtained for the convergence of the eyes are shown corrected so as to agree with the convergence of the targets during the ascending portion of the cycle. It will be noticed that, using the same calibration for the descending portion of the curve, the convergence of the eyes, as measured from the film, does not agree with the convergence of the targets. Yet in this portion of the cycle the convergence of the eyes must also have been identical with the target convergence, at least within the angle of a fixation disparity (minutes of arc).

This Figure also shows the second discrepancy, which is the more important one, namely, that when the target convergence reaches the normal setting, the measured convergence of the eyes falls below the target position, and yet the true convergence of the eyes must have been identical with that of the target convergence. This discrepancy was less with forced divergence than with forced convergence, and in the opposite direction, as shown in Figure 5. These two discrepancies, which are actually the same phenomenon, occurred in the same directions with nearly all subjects, regardless of the speed with which the forced convergence or forced divergence cycle was made. Apart from showing the discrepancy after the recovery point, the graphs also show the behavior of the eyes during the period of diplopia. In general, during the forced convergence cycle the eyes tend to maintain an esophoric position with considerable fluctuation, slowly in most subjects, although in some subjects rapidly, falling toward the phoria position.

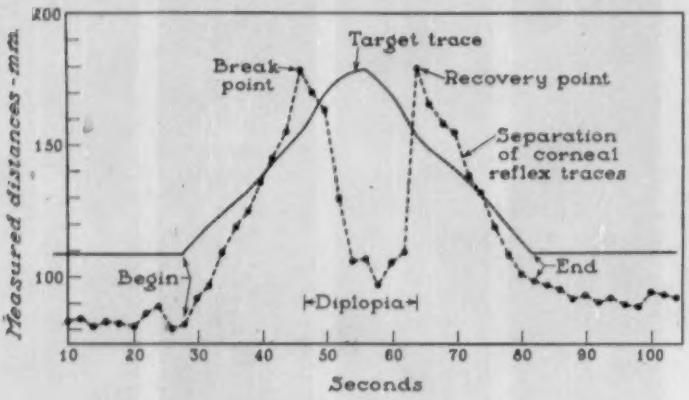

Fig. 3.—Raw data obtained from direct measurement on the projection of the film. The target trace is measured from the perforation line of the film.

At the phoria, or zero, position there was present at all times a small apparent irregular variation of the corneal intertrace about the convergence lines. This variation in equivalent convergence change ranged from 1.0 to 2.3 △, not only in the bilateral fixation experiments but even with unilateral runs. When records were made with only one eye fixing, small apparent oscillating fixation movements of the eyes at the phoria position were more evident than in records in which both eyes were fixing. When the target con-

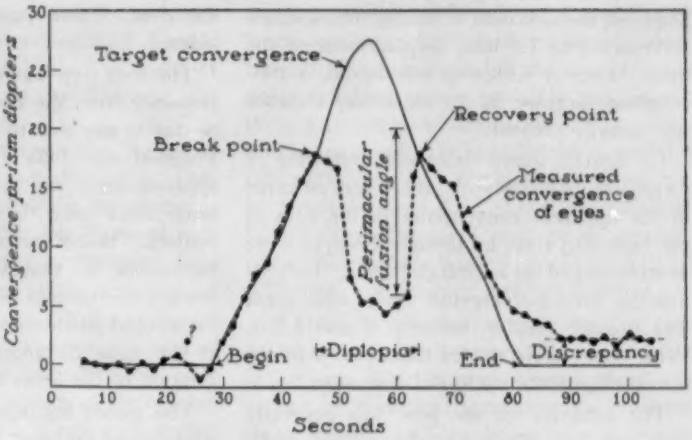

Fig. 4.—The data of Figure 3 corrected so as to be plotted in prism diopters. The data from the *begin* to the *break* point establish the calibration of the corneal-reflex separation in terms of convergence of the eyes. This calibration has been subsequently used for the data beyond the break point, though, obviously, these data points do not actually represent the convergence of the eyes.

vergence was increased, the apparent fixation oscillations or movements became smaller and a smoother corneal trace on the film was recorded. This effect was evident in both the unilateral and the bilateral tracings.

The eye-convergence traces generally followed the time-target-convergence traces well through the initial forced-convergence period up to the point of diplopia, or for a maximal convergence of about 20 Δ (ranging from 10 to 20Δ) in the instances in which diplopia did not occur. From this point, in both the unilateral (duction) and the bilateral fixation (disjunctive convergence) movements there appeared to be a gradually increasing discrepancy between the time-target-convergence trace and the corneal-image traces, although fusion was obviously still present. This is evident in the change in the calibration vergence slopes. The discrepancy ranged from 6 to 12 Δ in different subjects. During this part of the test, and with the greater degrees of convergence, a narrowing of the palpebral fissure and contraction of the pupil could be observed by the operator.

In some subjects the two corneal traces showed slight widening in both the unilateral fixation (duction) movements in the limits of medial and temporal directions and in forced convergence. This increase in width of the corneal-reflex trace on the film can be accounted for only by a change in the distances of the eyes from the camera lenses. By actual measurement with a shift of the

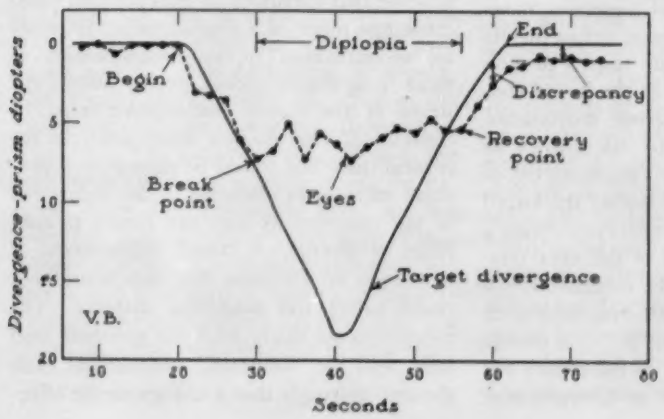

Fig. 5.—Similar results for the same subject whose data are shown in Figures 3 and 4, but for the forced divergence part of the test.

headrest, the maximal widening found would correspond to 1.5 mm. displacement of the head. When a widening was found, a concomitant increase in the intertrace distance was usually present.

In nearly every instance, following a forced-convergence cycle, there was an error in the apparent convergence of the eyes at the base-line zero, as though the eyes were overconverged between 0 and 2.4 Δ. Following the forced-divergence cycle, this error was usually smaller, between 0 and 1.5 Δ. With some subjects this discrepancy in the forced-divergence cycle did not occur.

The behavior of the eyes was generally different in the forced-divergence cycle. After diplopia took place, the eyes were steadier in that the convergent and divergent fluctuations were smaller. There were no definite or active searching-like movements of the eyes in an effort to regain fusion, as there were in the convergence tests. The recovery of fusion generally took place when the targets were converged and brought approximately to the point where diplopia initially occurred.

The pattern of convergence movements of the eyes varied in different subjects, as well as in the same subject at different times. No two identical corneal tracings were recorded, even though the external conditions, such as the lighting of the targets, the positioning of the head, and the movement of the arms of the haploscope, were the same.

It is clear that there was an intervening variable in the recording of these eye movements which caused the corneal-reflex images to change their position with respect to their original orientations prior to the forced convergence or forced divergence movements. One might account for this discrepancy by (1) a forward or backward displacement of either the eyes or the head during the forced convergence (or divergence) cycle; (2) a change in the visual axes of the eyes relative to the optic axes of the corneas; (3) a lateral displacement of both eyes nasally or temporally during the cycle, or (4) a change in the curvature or surface of the cornea due to the forced convergence or divergence of the eyes. These possibilities will be considered.

The first step was to see whether the discrepancy from the convergence traces could be due in any way to an instrumental factor. Polished steel balls (ball bearings), having approximately the same radius as the corneas, were used to replace the eyes of a subject. These were carefully mounted in the haploscope so that their anterior surfaces toward the camera were at what would be the normal positions of the corneas, and thus at the same distances from the centers of rotation of the arms of the haploscope.

The record tracings on the films obtained while using the steel balls were smooth and even, both in convergence and in divergence. The intertrace separation was always the same for the same convergence of the targets, irrespective of convergence or divergence movements.

The effect on the intertrace distance produced by a displacement of both balls backward or forward from the initial positions showed that each millimeter of displacement corresponded to an equivalent 1.6 Δ of convergence of the eyes. These measurements corresponded to those obtained with subjects in the haploscope when the headrest was displaced forward or backward. This also agrees with the calculations made on the basis of the geometry involved in the apparatus. A displacement of the balls also caused a widening of the traces on the film. With the present arrangement for supporting the head, it is not believed that variations in head position could cause this much of a displacement. Whether an enophthalmos or an exophthalmos of these magnitudes could occur under the stress of the forced convergence must be considered. The greatest discrepancy in the corneal-trace line would be caused by a very small increase or decrease in the separation of the two eyes as they are forced to converge or diverge. A lateral displacement of both eyes in the same direction would not really affect the intertrace distance. The measurements made with the polished steel balls and the theoretical calculations both showed strikingly that a change in the effec-

tive separation of the eyes produced a change in the corneal-reflex intertraces of 1 mm., corresponding to nearly 16 Δ. The width of the traces themselves on the film was unchanged.

The discrepancy between the measured intertrace separation and the actual convergence of the eyes could also be accounted for by assuming that the visual axis of each eye was changed relative to the optic axes of the corneas under the stress of the forced convergence or divergence. Park and Park ‡ assumed this actually to occur. However, such a change could be brought about only by a displacement or a tipping of the crystalline lens within the eye. While such a phenomenon is perhaps possible, so far there is little evidence to support the hypothesis.

It is well known that the curvature of the cornea departs from its spherical shape toward the limbus, where it becomes flatter. However, it is believed that none of the movements involved in this study would place the corneal-reflex image anywhere near those parts of the cornea which deviate greatly from sphericity. Nor would the variations of corneal curvature following advancement of the external horizontal muscles [6] and the changes of curvature of the cornea from contraction of the extrinsic muscles [7] be of sufficient magnitude to account for our results.

The evidence, therefore, at this point is that the discrepancies measured between the corneal-reflex intertrace separation and the actual convergence of the eyes can best be accounted for on the basis that (1) some enophthalmos or exophthalmos of the eyes occurs and (2) that the interocular separation changes slightly under the stress of the forced convergence-divergence movements. Effectively, this statement means that as the eyes move from a primary position, for example, each does not rotate about a fixed point but, rather, rotates about a point that follows a curve. For nasal movements not only would a forward or backward displacement of the eyes be found, but one could also expect an actual slight decrease in their effective separation. Obviously, we should like to have some other direct evidence of such nasal translatory movements, but the small magnitudes involved would probably not permit this. The maximal displacement found in this series of subjects was about 4 Δ, and the effect produced by a displacement of one eye by 1 mm. is 16 to 20 Δ. Thus, the maximal lateral displacement of one eye to account wholly for the discrepancy would be 0.12 to 0.10 mm., a magnitude difficult to detect.

A study of the literature shows that this problem has arisen before, namely, when eye movements have been photographed or observed by telescopic arrangements. Various incorrect explanations have been given to account for the results. In order to determine the characteristics of normal convergence and accommodative convergence, Clark [8] photographed the movements of the corneal reflex of the eyes of 20 university students whose eyes alternately fixated a near object and then a distant object. He reported on the basis of his photographs that errors of convergence of as much as 7 Δ could occur in these fixation movements and still fusion would be maintained! Obviously, we know that such errors of convergence cannot be attributed to Panum's areas of fusion, which are measured in minutes of arc. One must believe that Clark's results are due to the same discrepancy phenomenon reported in this paper. Clark did emphasize that wide individual differences were found in the behavior of the two eyes, as well as in successive performances of the same subject. This was true of both binocular and accommodative convergence.

Similarly, Peckham [9] observed the apparent rotation of the eyes through a telescope when one or both eyes were forced to converge, as in prism-vergence tests. He wrote that "binocular fusion was reported by the subject when the images of stimulated points failed to be anatomically corresponding by as much as 10 degrees in the extreme." He also found that the eye, before a fixed target, moved in the same direction as did the other eye when the latter was forced to move by a horizontal movement of an identical target.

‡ References 4 and 5.

This result cannot be explained in terms of retinal fusional areas, for the latter are much too small, in an entirely different order of magnitude. One must conclude that Peckham's apparent rotations or convergence errors were actually the same discrepancy phenomenon reported here.

More in line with the conclusions to be drawn from the present study are the investigations of Verrijp, Park and Park, and George, Toren, and Lowell.

Verrijp § measured the convergence movements of the eyes with the use of afterimages and concluded that there are a definite shift in the visual axes and a change in the position of the ocular center of rotation of the globe with those movements. He noted a retraction of the globe with unilateral (duction) movements and a greater degree of retraction with binocular convergence movements. He stated that the constant tonus of the muscles at the primary position is even greater than that when the eye changes fixation to a secondary position.

Park and Park || reported data to show that the center of ocular rotation cannot be fixed, and, moreover, that even during stationary fixation the angular relation of the visual and optic axes of the eye is not constant. They found that no norms could be established for different persons or even for the same person. They presented evidence that with changes in ocular position the point of rotation of the eye moves nasally and backward along a curve with changes in position. They concluded, however, that it would be unreasonable to suppose that the muscular pattern maintains the same lines of direction and the same relative quantities at all times in the absolute sense.

With very precise instrumentation, George, Toren, and Lowell [12] reported that, according to their measurements, when the eye is turned nasalward, it also invariably advances in the orbit, and when turned templeward, it recedes. When the eye turned 10 arc degrees the recession was 0.26 mm. and the advancement was 0.27 mm. When it turned 20 arc degrees, the recession was 0.49 mm. and the advancement was 0.59 mm. This direction of forward and backward displacement is just the opposite of that found by Verrijp.

Duke-Elder [13] wrote:

> Movement of pure translation normally permitted to the eye is small. If the tonus of the muscles is increased the eye is forced slightly backward; if the tonus of the muscles is lowered an exophthalmos is produced.

COMMENT

In any quantitative objective study of binocular eye movements it must be assumed that for the maintenance of fusion the images of the fixated object received by the two eyes fall on the corresponding foveas of the retinas, at least within the small angle of fixation disparity.[9] However, the centers of rotation of the globes themselves are not fixed. This fact introduces an error in any attempt to measure magnitudes of eye movements by any objective method of examining the eyeballs themselves or the reflected images from the corneas. These apparent changes are seen in the small, irregular saccadic movements with steady binocular fixation even when the eyes are in the primary position. More important, however, are the larger effects of movements of the eyes, such as enophthalmos or exophthalmos, nasal or temporal displacements of the globes, and perhaps even changes in the curvatures of the cornea. This does not exclude the possibility of changes in the visual axes with respect to the optic axis of the eye due to adjustments of the crystalline lens made by the intrinsic muscles of the ciliary body. In our experiments the corneal curvature cannot play a conspicuous role, for the images of the source light on the cornea were positioned too near the center of the cornea.

This increasing discrepancy between the corneal-reflex trace and the time-target trace with the maintenance of fusion may be due partly to enophthalmos. With unilateral fixation, the individual corneal-reflex trace is not widened to any appreciable extent, while with bilateral fixation the width of the individual corneal traces is measurably increased. An

§ References 10 and 11.

|| References 4 and 5.

enophthalmos may be present in the disjunctive convergent movements. This is in accord with the conclusions reached by Verrijp or George, Toren, and Lowell. However, there is a greater discrepancy in the corneal-reflex trace and the time-target trace with convergence than can be accounted for by an enophthalmos of the globes. If the enophthalmos accounted for the discrepancy, then the individual traces would have been much wider. One must assume that the greater part of the discrepancy is due to a slight nasal translation of the two globes in their orbits. The observed narrowing of the palpebral fissure, as well as contraction of the pupil, in conjunction with enophthalmos on convergence, has been reported as a retraction syndrome.¶

One cannot state positively that there was an enophthalmos present, for the widening of the individual corneal-reflex traces may be due to an exophthalmos. The measurements of George, Toren, and Lowell [12] showed that the eye invariably advances in the orbit when turned nasalward. The corneal-reflex intertrace distance would be narrowed by the exophthalmos, but a concomitant amount of nasal translation would easily account for the discrepancy between convergence obtained from the corneal-reflex traces and convergence indicated by the time-target trace.

It is to be noted that the convergence of the eyes within the initial 10 degrees usually followed the time-target trace, and the movements of the globes beyond this point revealed a change in the total picture. One can surmise that the check ligaments and orbital tissue are such that they permit, as well as stabilize, the eye movements within the usual amount (angular width) of binocular vision. With added medial rotation, and in a sense unusual vergence of the eyes, an abnormal additive stress is placed on the muscles in overcoming the resistance of the check ligaments and extraorbital tissue, thus changing the stress per unit rotation of the eye. Then, again, with increased medial rotation the oblique muscles enter their relatively greater field of action.

The contraction of the superior and inferior oblique muscles could cause a nasal translation of the globes, as well as exophthalmos. The functional origin of the superior oblique muscle is the trochlea, which is attached to the spina trochlearis on the under aspect of the frontal bone a few millimeters behind the orbital margin. The muscle bends downward, backward, and outward at an angle of about 55 degrees, passes under the superior rectus muscle, and is attached obliquely on the posterior superior quadrant, lateral to the midvertical plane of the globe. The inferior oblique muscle arises from a small depression on the orbital plate of the superior maxilla, a little behind the lower orbital margin and just external to the orifice of the nasolacrimal duct. The muscle passes outward and backward, making an angle of 50 degrees with the visual line (parallel with the reflected tendon of the superior oblique muscle), between the inferior rectus muscle and the floor of the orbit, then under the external rectus muscle, to be inserted on the back and outer portion of the globe, for the most part below the horizontal meridian.[16] The anatomic position of the oblique muscles is favorable to movement of the globe in its entirety in a nasal translation, as well as in an outward manner. The function of moving the globe in a translatory manner is unique and is distinct from the possibly concomitant rotational movement about the vertical axis and from the prime functions of the muscles, since elevation and depression of the globe are antagonistic and negate each other.

Following the disruption of fusion at the "break" point of forced convergence, there would be an immediate decrease in the tension of the medially rotating ocular muscles, and the convergence of the eyes would tend toward the phoria position. However, the tension does not drop immediately to normal, but slowly returns to that level. Hence, any slight lateral translation movement of the globe which occurs, owing to the tonicity of the muscles caused by the forced convergence, would remain for a time, but in

¶ References 14 and 15.

decreasing amount. The results here showed that the discrepancy at the zero position following the forced-convergence cycle tends to zero within a period of 4 to 20 seconds. However, there are many factors involved in this process, and one cannot assume even then that the muscles of the eyes have reached their primary tonus corresponding to the "rest," or phoria, position. Morgan,[17] indeed, has reported that in some instances the slow return of the eyes to the phoria position following forced convergence may take as long as 30 minutes. That the ciliary processes also contribute to the variation of the tonus of the extraocular muscles is suggested by the fact that with eyes into which homatropine had been instilled, relatively smoother eye movements were recorded by the corneal-reflex traces. The individual corneal traces reveal a relatively even width throughout the convergent movement in both the duction and the disjunctive convergence tracings, supporting Verrijp's conclusions "that with active accommodation there was also a retraction of the eyes. The retraction arises because of the changes in the accommodative-convergence mechanism."

The increased amount of binocular convergence possible with the release of the accommodative factor supports Tait's observation [1]: "Excessive accommodative convergence is not unusual in examinations under cycloplegia, particularly homatropine." Others have pointed out that the accommodative convergence mechanism is reciprocal in association and diplopia occurs with convergence of the eyes, accommodation being the limiting factor. Near the limiting point of increased binocular convergence, there is a rapid increase in the accommodative innervation, causing a blurring of the target and subsequent diplopia because fusion is no longer being maintained.

SUMMARY

On the basis of the data collected in this study, it is concluded that a precise objective measurement of eye movements by photographic or telescopic observation of details on the eyes themselves or of images from light reflected from the corneas is not possible. Even if one were to obtain a corrected calibration curve for the discrepancies found, the variability in apparent positions of the eyes after the point of diplopia has been reached in the forced convergence would prevent one from obtaining a precise measure of the relative amount of convergence of the eyes as compared with convergence of the targets of the haploscope, and thus a measure of the extent of perimacular fusional areas. All this is apart from the role that may be played by the psychic factor of the voluntary effort to converge at the recovery point.

A haploscope was combined with an ophthalmograph camera, the latter being so modified that on the film there is also a simultaneous record of the convergent position of the arms of the haploscope. With this arrangement it was hoped that one could obtain a continuous record of the convergence of the eyes from the photographed corneal-reflex images, with the actual convergence of the test targets. This record would be useful in studying the behavior of the eyes as they were forced to converge or diverge through the "break" and "recovery" points, and in particular to determine the disparity of the two targets at the moment of recovery.

An intensive study has shown, however, that a precise measurement of the actual convergence of the eyes is not possible, owing to a displacement of the corneal-reflex images associated with the eye movements. This discrepancy has been discussed from the point of view that the eyes do not turn about fixed axes, but move along curves associated with translatory displacements. It was proved that if the eyes turned about a fixed axis (steel balls) a precise measure was obtained. With convergence the importance of possible nasal displacements of the eyes is stressed, and the unique synergistic function of the oblique muscles of nasalward and outward movement of the globe is presented. The tonic states of the extraocular muscles, as modified by forced convergence or divergence and accommodative reflexes, introduced a variability in

these translatory displacements that prevented the determination of a precise lawful behavior of the eyes under conditions of stress.

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Transillumination Through Everted Lid to Visualize Foreign Bodies

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In the past year I have seen four patients who have had vegetable spines or bracts lodged in the conjunctival sac, with marked symptoms of scratching, lacrimation, etc., which characterize a sharp foreign body rubbing on the cornea.[1]

These tiny bracts have barbs on them and tend to stick firmly in the conjunctival aspect of the eyelid. Being vegetable matter, they are very hard to see. By accident I found a way to visualize them more easily, and I felt this information worth passing on.

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The first case of this sort was relieved when I finally, with difficulty, located the foreign body with the use of the slit lamp. I was able to remove it with fine forceps. In the second case I failed to see the foreign body on everting the lid, using a loupe and a good light. Looking again, I everted the upper lid with a Finoff transilluminator tip and unintentionally left the transilluminator light on while doing so. The light shone through from behind the everted lid, and the barb could be seen in contrast, sharp and dark, against the brightly glowing tissues.

Fig. 1.—The transilluminator tip, with light on, is held behind the everted lid.

Fig. 2.—Vegetable spine which had been embedded in the conjunctival surface of the upper lid for nine days. Magnification approximately 80 ×.

While an assistant held the transilluminator tip behind the everted lid, I was able to pluck out the foreign body, and the patient was cured.

This worked very well in the third case. The fourth case is described here.

REPORT OF A CASE

E. C., a 63-year-old rancher, was working out-of-doors on Sept. 28, 1955. It was a windy day. "Something sharp" hit him in the right eye. He felt intense discomfort and a sense of scratching whenever he blinked the eye. In the ensuing nine days he went to two medical doctors and to an optometrist, trying to get relief. No foreign body was seen by these men. I was the fourth man to give him attention. He came to my office on Oct. 7. The eye was very red. The globe was definitely soft to palpation. The cornea showed many superficial linear abrasions. There was no evidence of uveitis. When the everted upper lid was transilluminated, the foreign body was easily seen. The patient was enormously relieved the moment the barb was plucked out with fine forceps.

Figure 1 shows the manner in which the transilluminator tip is held behind the everted upper lid. Figure 2 is a photomicrograph of the barbed bract which was removed in the case just described.

This means of helping to visualize a foreign body may be well known to many, but I have never read about it or seen it used by anyone else.

628½ Sixth St.

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Ocular Involvement in Multiple Myeloma

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In about one-fourth to one-third of the cases of fatal multiple myeloma there is infiltration of characteristic myeloma cells in the viscera or other soft tissues.[1] Almost any part of the body may be susceptible. Infiltrations have been found in the kidneys, liver, heart, skin, subcutaneous tissue, tonsils, thyroid, testes, ovaries, pleura, gastrointestinal tract, pancreas, uterus, adrenals, and dura.* This paper reports the occurrence of myelomatous infiltrates within the vascular and fibrous tunics of the eye.

In 1918, Stock[3] reported a myeloma of the choroid in an eye which was enucleated during life. This was a heavily vascularized tumor, replacing part of the posterior choroid and extending from the disc almost to the lens. The tumor was encapsulated by fibrous connective tissue, with degeneration of the overlying retina. The predominant cell was described as similar to the plasma cell. The concomitant diagnosis of multiple myeloma was not established. This tumor is denoted by Clarke[4] as the only instance of a myeloma of the inner eye. The other ophthalmic complications of multiple myeloma, as reviewed by Clarke,[4] include retinal hemorrhages, thrombosis of the central retinal vein and central retinal artery, papilledema, ocular nerve palsies, orbital myeloma, and involvement of the optic pathways. No references were found in the ophthalmic literature which describe the occurrence of myeloma-cell infiltrates within the eye in multiple myeloma.

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From the Department of Ophthalmology and the Eye Laboratory of the Montefiore Hospital.

* References 1 and 2.

REPORT OF A CASE

History.—A 50-year-old Negro woman was admitted with a history of back pain of five years' duration. There was tenderness over the ribs, lower half of the sternum, lumbar spine, and sacrum. Eye findings were not reported. X-rays revealed rarefaction of the skull, fractures of several ribs, and compression fractures of two vertebrae. Bone marrow examination revealed 17% plasma cells. There was a consistent Bence Jones proteinuria. The serum albumin was 4.6 gm/100 cc., and serum globulin, 1.9 gm/100 cc. The peripheral blood and blood chemistry determinations were unremarkable. A cave-in of the rib cage later occurred, resulting in paradoxical respiration. The patient died in a respirator, with the clinical diagnosis of multiple myeloma and evidence of renal disease.

Necropsy.—Sections of the calvaria revealed osteolytic changes. Multiple fractures of the ribs were present. The vertebral bodies were largely replaced by soft tumor tissue. The remainder of the examination revealed no notable abnormalities.

Histologic Findings.—Myeloma-cell infiltrates were found in the liver, spleen, adrenals, bone marrow, vertebrae, calvaria, dura, and eye. The kidneys contained masses of polymorphonuclear leucocytes in the renal tubules and cortex. Anatomical diagnosis was multiple myeloma, with involvement of liver, spleen, adrenals, dura, and eye, and suppurative pyelonephritis.

Eye Findings.—The globes were normal in size and shape. The choroid was heavily pigmented. Cystic degenerative changes were present at the peripheral retina. There was partial atrophy of the optic nerve fibers in both eyes, with considerable glial proliferation.

Within the iris and choroid of the left eye, and in the sclera of the right eye, there were deposits of small cells, round or oval in shape, slightly larger than lymphocytes. The cells were basophilic with pale-staining cytoplasm. The nuclei were eccentrically placed, with a spoke-like arrangement of the nuclear content (Fig. 1). The cells were insinuated without any special arrangement in the iris at its base, well within the stroma and extending to the anterior iris surface (Fig. 2). Many of the cells were free in the anterior chamber, with some cells adherent to the posterior corneal surface (Fig. 3).

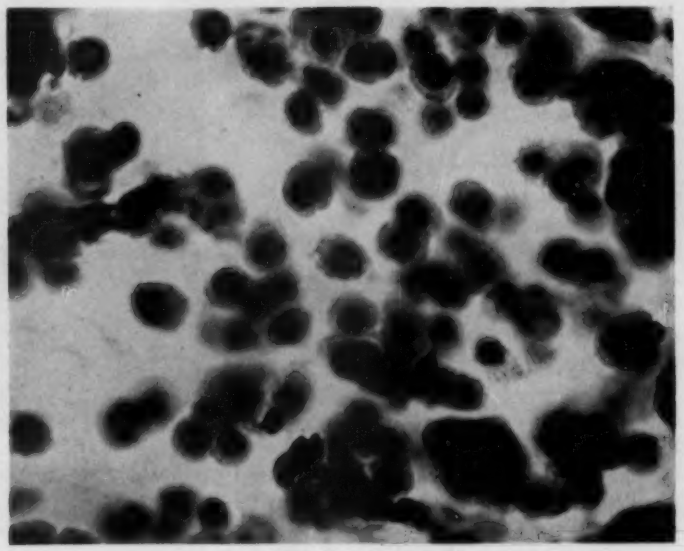

Fig. 1.—Higher magnification of iris infiltrate. Cells are round or oval, with abundant cytoplasm. Nuclei are eccentric with cartwheel structure. Reduced to ⅔ of mag. × 600.

Other cells were upon and within the meshwork of the iris angle (Fig. 4). Another deposit of cells was located about a posterior ciliary vessel in the sclera of the right eye (Fig. 5). Not photographed was a small infiltrate in the posterior choroid of the left eye. Russell bodies were not found.

Comment.—These cellular colonies are characteristic of a plasma-cell myeloma. Similar cellular deposits were found in the liver, spleen, adrenals, bone marrow, vertebrae, calvaria, and dura. Morphologically myeloma cells are indistinguishable from immature plasma cells, and transitions from immature myeloma cells to typical mature plasma cells are observed.† The plasma cell has been described as having these features: abundant cytoplasm of round, oval, or polygonal form; an eccentric nucleus; a paranuclear, lightly stained vacuole, and a small nucleus with deeply stained chromatin blocks arranged in a circle about the nuclear membrane.‡ The nucleus often resembles a cartwheel.§

† References 2 and 5.

‡ von Marschalko, T., cited by Michels.[6]

§ Pappenheim, A., cited by Stout and Kenney.[11]

Fig. 2.—Iris infiltrate of myeloma cells at the iris root and angle of the anterior chamber (arrow). Reduced to 63% of mag. × 120.

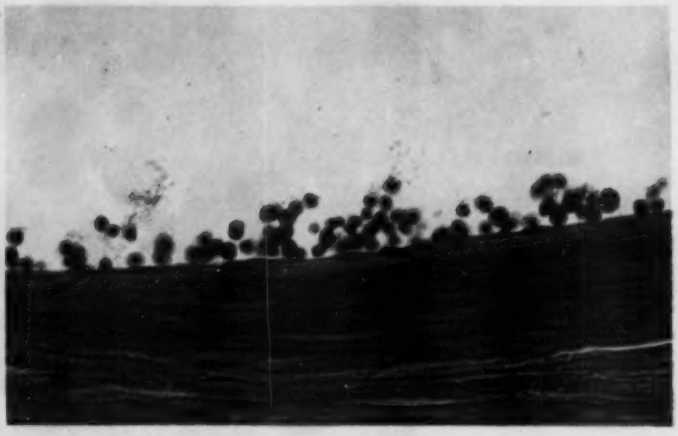

Fig. 3.—Section of posterior cornea and anterior chamber showing clusters of myeloma cells adjacent to the corneal endothelial surface. Reduced to ⅔ of mag. × 360.

The features distinguishing these infiltrates from a nonspecific plasma-cell reaction are the degree of cellular immaturity, the absence of a compact group of cells, and the absence of a macrophagic reaction.‖ Inflammatory plasma cells show a tendency to be arranged around capillaries and are usually associated with a marked increase in macrophages.¶

One other case of multiple myeloma was available for review in which autopsy was performed, and in which the eyes were obtained post mortem. Slides of both eyes of this case were reexamined, with no evidence of infiltration of myeloma cells.

‖ References 5 and 7.

¶ Sundberg, D., cited by Breitenbucher and Hertzog.[7]

GENERAL COMMENT

Multiple myeloma is usually regarded as a malignant tumor arising in the bone marrow.[5] Multiple lesions in the flat bones containing red marrow are the usual features.[5] Extraskeletal deposits of tumor cells are frequently found in soft tissues.[1] Whether these extraskeletal infiltrates are metastatic or are local in origin remains uncertain, for it is possible that the tumors in the spleen, liver, and lymphoid tissue originate in these hema-

Fig. 4.—Magnified view of the anterior chamber angle. Arrows point to myeloma cells upon and within the meshwork of the iris angle. Reduced to 62% of mag. × 120.

Fig. 5.—View of posterior segment of the choroid and sclera. Arrow points to an infiltrate of myeloma cells in the sclera, about a posterior ciliary vessel. Reduced to 62% of mag. × 120.

topoietic areas.[1] Infiltration of the eye is, more than likely, metastatic. Reese and Blodi[9] have recently described the eye as possessing a hematopoietic potential. Uveal infiltration, then, might be regarded as a resumption of local blood-making activity.

When an isolated tumor consisting of plasma cells is found, there arises a problem as to whether this is a primary plasma-cell tumor or a lesion representing multiple myeloma. The primary plasma-cell tumor, plasmacytoma, or plasmoma,[10] is a neoplasm consisting essentially of solid masses of plasma cells.[11] Usually solitary, the primary plasma-cell tumor is most frequently encountered in the air passages and conjunctiva.[12] Rare occurrences have been described in the orbit,[13] lacrimal sac,[10] lids, and caruncle.[12] Myeloma also has been reported in the orbit.[14] The diagnosis of primary plasma-cell tumor is reinforced when the tumor is confined and there is no other clinical evidence of multiple myeloma. It is probable that multiple myeloma, plasmacytoma, and plasma-cell leukemia are all different manifestations of one disease.#

Myeloma cells can gain access rather easily to the blood stream, resulting in the occasional plasma-cell leukemia, or, more logically, a "myeloma cell leukemia."[2] In the present case repeated peripheral smears failed to demonstrate circulating myeloma cells, but the resemblance of the cell deposits to leukemic infiltrates is noteworthy. Granulocytic and lymphocytic leukemic infiltrates are encountered frequently in the eye.[10] They are found oftener in the posterior choroid but may be located in the anterior choroid and retina as well.[10] Leukemic infiltrates, too, are found in many organs, such as the lung, heart, kidneys, and skin.[1] There is an obvious similarity in the colonization of infiltrates in leukemic disease and in myeloma. The similarity is further extended to the eye with the demonstration of similar-type infiltrates in the same susceptible tissues.

SUMMARY

A case of myeloma-cell infiltration of the sclera, choroid, and iris is reported. Myeloma-cell infiltrates have previously been reported within almost every other body structure. The infiltrates are differentiated from a nonspecific inflammatory process. A similarity between leukemic and myelomatous infiltrates is noted.

Dr. Samuel Gartner, Director of the Department of Ophthalmology, Montefiore Hospital, gave helpful advice in this study. The photography is the work of Mr. Antol Herskovitz.

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Perfusion Studies on the Outflow of Aqueous Humor in Human Eyes

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and
A. NEETENS, M.D., Ghent, Belgium

The tonography studies of Grant * have shown clinically the importance of the outflow of the aqueous humor. It is the decrease of the outflow in wide-angle glaucoma that is especially interesting.

Normally, the average value for outflow of aqueous humor per millimeter Hg per minute (C) is 0.24 cu. mm. according to Kronfeld,[11] 0.23 cu. mm. according to Grant [9] and Mansheim,[12] and 0.22 cu. mm. according to Weekers and Prijot.[16]

The resistance to the outflow of aqueous humor (R) is inversely proportional to the value of C, that is, $1/C$. According to Weekers, Watillon, de Rudder, and Lustin (1955), the average values of R are 3.7 for ages less than 35 years, 4 for ages between 35 and 55, and 4 for ages past 55.

In wide-angle glaucoma, Weekers and Prijot † found in a series of eyes the ocular tension of which was less than 26 mm. 0.028 and 0.168 cu. mm. as extreme values of C and in a series of eyes the ocular tension of which was greater than 26 mm., 0.017 and 0.119 cu. mm., so that the average value of C was 0.10 cu. mm. and that of R 10. Mansheim [12] found the same values.

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Researcher of the National Funds for Scientific Research (Dr. Rabaey).

From the Ophthalmological Clinic of the University of Ghent; Director, Prof. J. François, M.D.

*References 7 and 8.

†References 14 and 18.

Bárány [1] (1954) obtained by perfusion of enucleated rabbit eyes values for C fully concordant with those obtained by other methods. In a series of 29 enucleated eyes, the average value of C was 0.187 cu. mm., that is to say, an outflow of aqueous humor of 2.75 to 3 cu. mm. per minute for an ocular tension of 20 mm. Hg. These experiments demonstrate that the resistance to the outflow depends only on anatomical conditions and that it is not influenced by physiological modifications, such as the circulation of the blood.

On the other hand, Bárány [2] (1954), and Watillon, Prijot, and Weekers [17] by perfusion of enucleated rabbit and cattle eyes, demonstrated that hyaluronidase caused a lowering of the resistance to the outflow of nearly 50%. While our own work was approaching completion, we learned that Grant [10] (1955) had perfused 31 human eyes with isotonic salt solution and had found a value of 0.208 cu. mm. for C and, after viscosimetric correction to 37 C, a value of 0.27 cu. mm., a value which is above the average for C of 0.233 cu. mm., obtained by tonography on 171 normal eyes.

On the contrary, in an eye enucleated for melanosarcoma tonography gave a value for C of 0.30 cu. mm. and by perfusion 0.29 cu. mm.; these results agree perfectly. After perfusion of an enucleated human eye, an enucleated monkey eye, and a living monkey eye, Perkins [13] (1955) obtained values for C of 0.11, 0.80, and 0.625 cu. mm., respectively. After opening Schlemm's canal *ab externo*, leaving the trabeculum intact, he found a decrease in resistance; i. e., C values were 0.39, 1.88, and 2.59 cu. mm., respectively.

PERSONAL RESEARCH

After having repeated Bárány's perfusion experiments with rabbit eyes, we applied the same technique to enucleated human eyes in order to study the outflow of the aqueous humor before and after treatment with hyaluronidase.

In order to obtain morphological information concerning the manner of outflow of the perfusion fluid, we added India ink or colloidal Thorotrast and examined the eyes, especially the iridocorneal angle, histologically after serial sectioning and with the aid of microradiograms.

We were particularly struck by the considerable influence of the depth of the anterior chamber on the facility of the outflow, and this we studied systematically.

Eventually, we had the opportunity to perfuse eyes affected by glaucoma simplex and secondary glaucoma.

TECHNIQUE

Our technique was nearly the same as that of Bárány (1953). We always used the same water pressure, 27 cm., for rabbit eyes.

Corrections for the capillarity of the pipettes used were made; the perfusion solution was prepared by mixing one part of Sörensen's phosphate buffer solution, of pH 7.1, with nine parts of saline.

The India ink was always added in the proportion of one part of ink and two parts of perfusion fluid; on the other hand, Thorotrast was added without dilution.

The amount of hyaluronidase was always 20 V. R. U. For the rabbit eyes we used Enzodase (Squibb), and for the human eyes, hyaluronidase (H. Chibret et fils).

The human eyes, for the most part from patients past 50 years of age, were enucleated two to three hours after death. Some eyes were obtained after enucleation for melanosarcoma of the choroid; these eyes were perfused immediately after enucleation to prevent evaporation.

During the experiment the globes were surrounded with pieces of cotton soaked in saline. We worked at room temperature, about 20 C.

In order to verify the influence of the depth of the anterior chamber on the resistance to the outflow, we applied at the equator of the globe a guillotine-pincette with regulatable opening; this permitted us to decrease or increase, as we wished, the volume of the globe and the depth of the anterior chamber.

With the aid of a slit lamp and a binocular microscope, provided with a micrometric scale graduated in tenths of a millimeter and nonius, we were able to obtain a measure of the depth of the anterior chamber. Corrections were made for the error due to the refraction of the cornea.

RESULTS

1. *Experiments on rabbit eyes.*‡

We perfused 62 rabbit eyes and obtained an average value for *C* of 0.21 cu. mm.

‡ Part of this work was done by one of us (M. R.) in The Johns Hopkins University School of Medicine, under Prof. J. Friedenwald, M.D., as a Fulbright grantee in November and December, 1954.

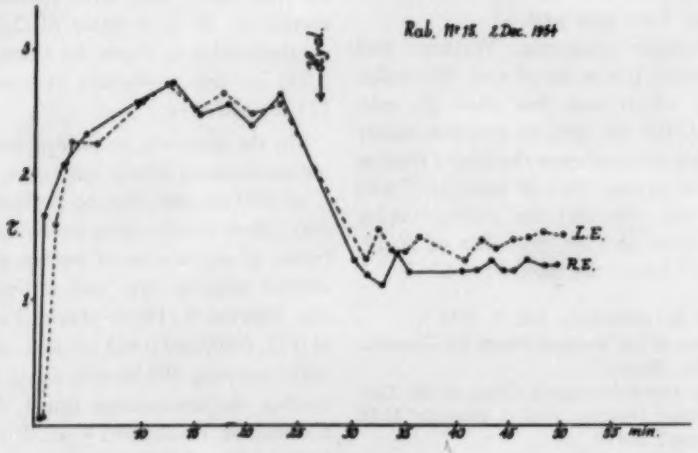


Figure 1

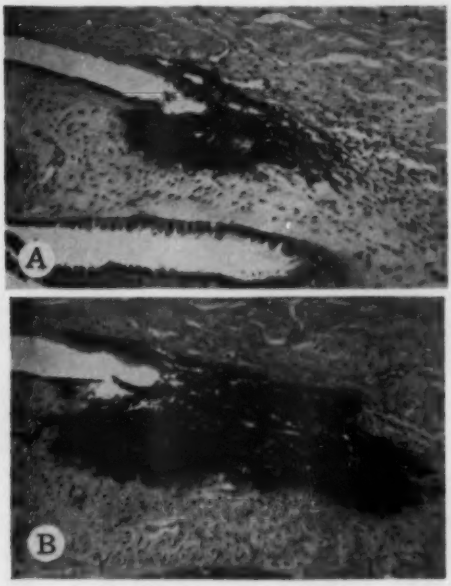


Fig. 2.—Hematoxylin-eosin stain (obj. 8 mm.; ocul. 8 ×). See text.

(R=4.7). After perfusion with hyaluronidase the increase for C was generally of the order of 40% to 50% (Fig. 1). The principal purpose of these experiments was the histological examination of the eye perfused with India ink.

Without hyaluronidase, we found India ink only in the scleral trabeculum and the intrascleral plexus (Fig. 2*A*), demonstrating that this is the way of outflow of the perfusion fluid.

After addition of hyaluronidase, the same scleral trabeculum and the tissues of the iridocorneal angle were much more infiltrated (Fig. 2*B*), demonstrating that they became much more permeable.

The microradiograms, after injection of Thorotrast, gave excellent confirmation of these results.

After the angle was scraped over a circumference of about 90 degrees, the resistance to the outflow decreased considerably (Fig. 3). Histological examination permits us to make sure that the intervention was really a withdrawal of trabecular tissue and not a cyclodialysis. Perilimbal incisions, on the contrary, have no influence on the facility of outflow.

2. Experiments with Human Eyes.

(*a*) Before Treatment with Hyaluronidase: We perfused 67 human eyes. Figure 4 illustrates and Figure 5 shows the distribution of our results, which are presented in Table 1. They are, again, in agreement with the values obtained clinically by tonography. Indeed, the average value of C is 0.25 cu. mm., the maximal value being 0.60 and the minimal 0.12 cu. mm., resulting in an average value for R of 4, with a maximal value of 8.3 and a minimal of 1.66.

(*b*) After Treatment with Hyaluronidase: Twenty-four eyes were also perfused with hyaluronidase solution (Figs. 4 and 5). The first thing we noticed was that the effect of the hyaluronidase in humans was considerably less than in animals; indeed, the average value of the decrease in resistance was between 25% and 30% in humans and 40% and 50% in rabbits.

The second observation was that the effect of the hyaluronidase was more variable in humans. The maximal value of decrease in resistance was 66% (No. 23), and the minimal, 5% (No. 25). In two cases we even observed an increase in resistance, or a reverse action of the enzyme (12.5% increase, No. 30, and 5% increase, No. 36). It is

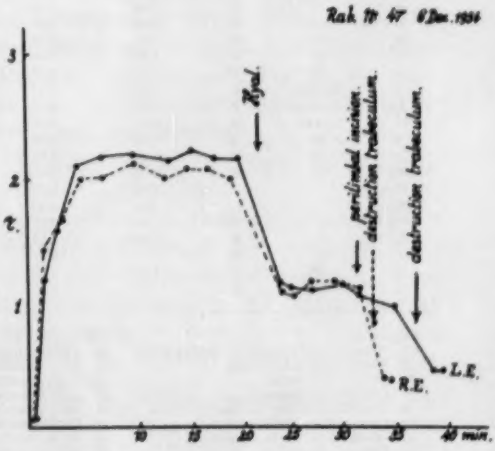


Figure 3

TABLE 1.—*C and R Before and After Treatment with Hyaluronidase*

Eye No.	Age	Sex	Before Treatment: Average Time Outflow 10 Cu. Mm.	Before Treatment: Cu. Mm./ Min./Mm. Hg (*C*)	Before Treatment: Resistance (*R*)	After Treatment with Hyaluronidase: Average Time Outflow 10 Cu. Mm.	After Treatment with Hyaluronidase: Cu. Mm./ Min./Mm. Hg (*C*)	After Treatment with Hyaluronidase: Resistance (*R*)
1	49	M	1'40"	0.30	3.33			
2	49	M	1'50"	0.28	3.6	1'20"	0.37 (+33%)	2.7
3	66	M	60"	0.50	2			
4	66	M	69"	0.43	2.3	61"	0.5 (+17%)	2
5	64	M	78"	0.31	3.2			
6	64	M	52"	0.58	1.7	41"	0.71 (+22%)	1.3
7	71	F	4'10"	0.12	8.3			
8	71	F	4'10"	0.12	8.3	2'58"	0.16 (+33%)	6.2
9	57	M	3'48"	0.13	7.7			
10	57	M	2'50"	0.18	5.5	2'14"	0.22 (+22%)	4.5
11	61	F	9'	0.05	20			
12	55	M	1'43"	0.29	3.4			
13	55	M	1'20"	0.37	2.7	50"	0.60 (+62%)	1.67
14	52	M	1'26"	0.35	2.8			
15	52	M	1'8"	0.43	2.3	54"	0.56 (+30%)	1.7
16	76	M	3'18"	0.15	6.6			
17	76	M	2'32"	0.19	5.2	2'13"	0.22 (+16%)	4.5
18	62	F	1'52"	0.26	3.8			
19	62	F	1'55"	0.26	3.8	1'40"	0.30 (+15%)	3.33
20	48	F	1'40"	0.30	3.33			
21	48	F	2'15"	0.22	4.5	1'28"	0.34 (+55%)	2.8
22	67	M	50"	0.60	1.67			
23	67	M	2'20"	0.21	4.7	1'22"	0.35 (+66%)	2.8
24	57	F	2'36"	0.19	5.2			
25	57	F	2'25"	0.20	5	2'20"	0.21 (+ 5%)	4.7
26	11 mo.	F	2'10"	0.23	4.3			
27	id.	F	2'28"	0.20	5	2'15"	0.22 (+10%)	4.5
28	56	F	2'30"	0.21	4.7			
29	30	M	2'10"	0.23	4.3			
30	30	M	2'12"	0.23	4.3	2'25"	0.20 (—12.5%)	5
31	31	M	3'10"	0.15	6.6			
32	31	M	4'10"	0.12	8.3	2'50"	0.18 (+50%)	5.5
33	76	F	2'45"	0.18	5.5			
34	76	F	2'	0.25	4	1'25"	0.35 (+40%)	2.8
35	46	M	2'	0.25	4			
36	46	M	2'20"	0.21	4.7	2'30"	0.20 (— 5%)	5
37	55	F	2'15"	0.22	4.5			
38	55	F	1'50"	0.28	3.6	1'30"	0.33 (+18%)	3
39	68	M	2'10"	0.23	4.3			
40	68	M	1'35"	0.31	3.2	1'15"	0.40 (+28%)	2.5
41	55	F	2'	0.25	4			
42	55	F	1'40"	0.30	3.33	1'20"	0.37 (+25%)	2.7
43	71	M	2'15"	0.22	4.5			
44	71	M	2'10"	0.23	4.3	1'30"	0.33 (+38%)	3
45	56	F	2'	0.25	4			
46	56	F	2'5"	0.24	4.1	1'30"	0.33 (+40%)	3
47	4	M	1'35"	0.31	3.2			
48	4	M	1'25"	0.35	2.8	1'10"	0.43 (+22%)	2.3
49	61	F	2'40"	0.19	5.2			
50	61	F	1'50"	0.28	3.6			
51	23	M	1'45"	0.21	4.7			
52	41	M	2'5"	0.24	4.1			
53	68	F	1'40"	0.30	3.33			
54	72	M	1'55"	0.26	3.8			
55	14 days	F	2'55"	0.17	5.9			
56	14 days	F	3'5"	0.16	6.2	2'16"	0.23 (+43%)	4.3
57	2 days	M	2'	0.25	4			
58	64	M	1'55"	0.26	3.8			
59	62	F	2'47"	0.16	6			
60	62	F	3'35"	0.14	7			
61	..	..	3'25"	0.15	6.6			
62	..	..	2'10"	0.23	4.3			
63	87	M	7'45"	0.07	14			
64	42	F	2'45"	0.18	5.5			
65	42	F	3'	0.17	5.9			
66	63	M	1'20"	0.37	2.7			
67	63	M	55"	0.57	1.8			

* Eye No.
7 Anatomical lesions in trabeculum
11 Wide-angle glaucoma
26 Congenital cataract
27 Congenital cataract
28 Enucleation for melanosarcoma
29 Generalized body edema
30 Generalized body edema
35 Uremia (coma)
36 Uremia (coma)

Eye No.
49 Thrombosis central retinal vein
51 Ant. chamber depth, 1.4 mm.
52 Ant. chamber depth, 3.5 mm.
53 Ant. chamber depth, 1.2 mm.
54 Ant. chamber depth, 2.8 mm.
55 Hydrocephalus
56 Hydrocephalus
60 Ant. chamber depth, 1.3 mm.

Eye No.
61 Ant. chamber depth, 3.2 mm.
62 Ant. chamber depth, 1.8 mm.
63 Rubeosis iridis; secondary glaucoma
64 Ant. chamber depth, 2.1 mm.
65 Ant. chamber depth, 1.5 mm.
66 Ant. chamber depth, 3.7 mm.
67 Ant. chamber depth, 3.6 mm.

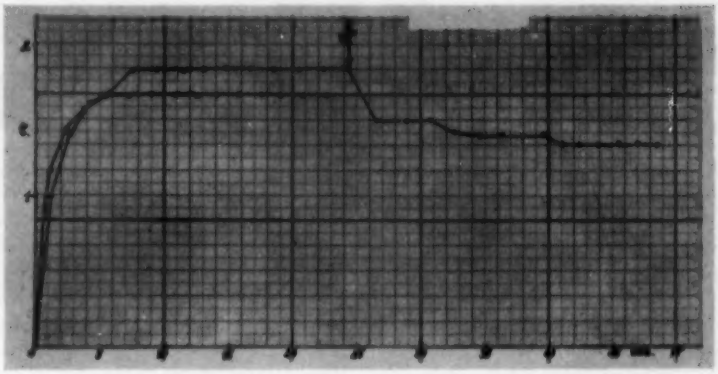


Figure 4

remarkable that these three cases (25, 30, 36) were of patients who had general edema and died of uremia.

Histological sections of the eyes perfused with India ink show that the perfusion fluid actually leaves the anterior chamber through the scleral trabeculum, Schlemm's canal, and the intrascleral plexus, but very fine ink particles are also found in the iris stroma and the inner part of the ciliary body, where it arrives simply by diffusion.

Microscopic examination did not reveal any obvious difference before or after treatment with hyaluronidase (Fig. 6*A* and *B*).

On the contrary, the microradiograms § made after perfusion with Thorotrast showed some difference; indeed, the contrast substance was present more profusely in the trabeculum after treatment with hyaluronidase than before (Fig. 7*A* and *B*), the reticular pattern was better determined; the limits of the clefts were more distinct; the diffuse aspect tended to disappear; the strips corresponding to the clefts were more elongated, and, in some places, transverse streaks predominated.

These patterns seem to indicate a certain enlargement of the clefts. This enlargement, however, is not of great importance, since Angiopac particles of 2.25μ do not pass through the trabeculum before or after treatment with hyaluronidase.

3. *Modifications of Depth of Anterior Chamber.*

It seems evident that only at the moment of complete closure of the angle is the facility of outflow decreased considerably, even to complete extinction, and that as long as the smallest cleft between iris and cornea remains, the outflow continues normally.

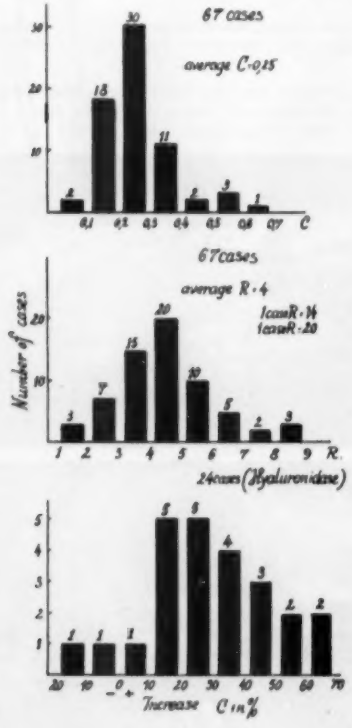


Figure 5

§ These examinations were performed in collaboration with Dr. J. M. Collette, assistant to the laboratory of roentgenologic diagnosis of the University of Liége (Director, Prof. Dr. G. Leroux).

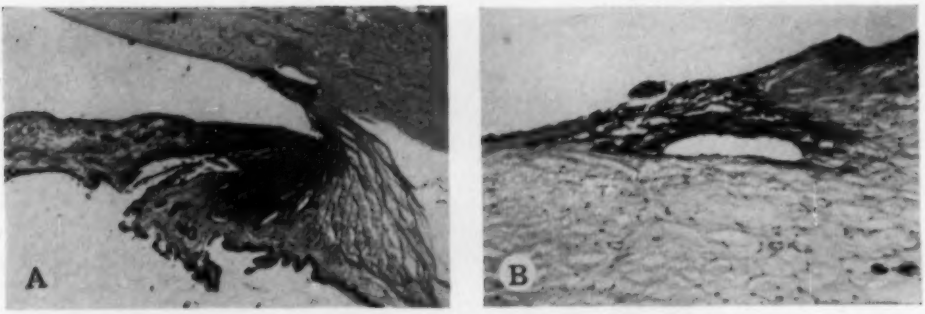


Fig. 6.—*A*, hematoxylin-eosin stain (obj. 1 mm.; ocul. 8 ×). *B*, hematoxylin-eosin stain (obj. 16 mm.; ocul. 8 ×). See text.

Figure 8, relating to seven cases, demonstrates, on the contrary, that this conception is not exact and that the degree of depth of the anterior chamber is of great importance.

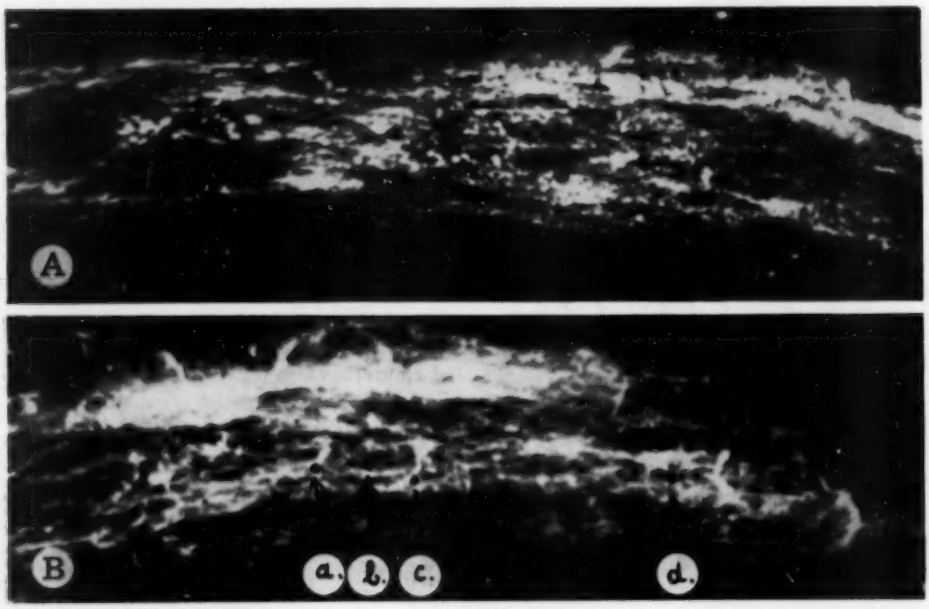
In Figure 8 is plotted as the abscissa the depth of the anterior chamber and as the ordinate the number of minutes necessary for 10 cu. mm. of perfusion fluid to escape from the anterior chamber under a water

TABLE 2.—*Relation of Aqueous Outflow Rate to Depth of Anterior Chamber*

Depth of Anterior Chamber, Mm.	Resistance to Outflow (*R*)
4.4	3.33
3.6	4.7
2.2	8.3
2.2	9
1.4	16
0.7	25

Fig. 7.—*A*, inner wall of Schlemm's canal. Injection of Thorotrast into the anterior chamber without treatment with hyaluronidase. Trabecular pattern and numerous white spots; diffuse general aspect. × 75.

B, inner wall of Schlemm's canal. Injection of Thorotrast into the anterior chamber after treatment with hyaluronidase. Reticular pattern more obvious with larger clefts (*a* and *b*); transverse streaks appearing (*c*); contrast substance more conspicuously present (*d*). × 75.



pressure of 27 cm., for a given depth of chamber. The deeper the anterior chamber the higher the rate of outflow, and the shallower the anterior chamber the lower the rate of outflow. As an example, the results for Case 52 are shown in Table 2.

By varying the depth of the anterior chamber, as much in one sense as in another, it is possible to modify at the same time and in the same proportion the rate of outflow, this phenomenon being entirely reversible. On the other hand, for a determined depth in the same eye, the same rate of outflow is always obtained. In the rabbit, the same correlation between chamber depth and rate of outflow is also obtained.

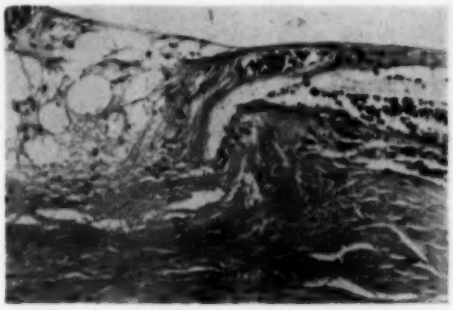


Fig. 9.—Hematoxylin-eosin stain (obj. 16 mm.; ocul. 8 ×). See text.

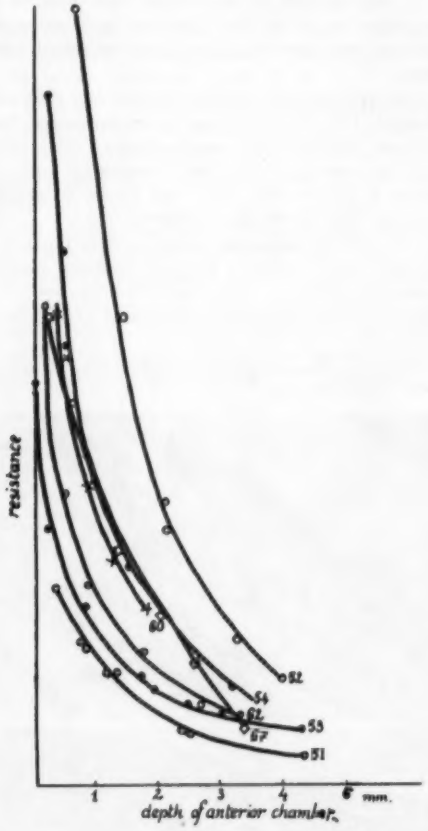


Fig. 8.—The numbers refer to the resistance values of the curves for decreasing depths of the anterior chamber.

No. 51	1	1.7	1.8	3.5	3.6	4.3	4.5	6.3
No. 52	3.33	4.7	8.5	9	15	25	...	...
No. 53	1.7	2.3	2.4	3	3.3	5.5	9.3	12.9
No. 54	3.2	6.8	14.3	16.8	22.2	...	...	...
No. 60	5.5	7	9.5	13.7	15.1	...	...	...
No. 62	2.3	2.7	4.3	6.7	9.3	15.3	...	...
No. 67	1.7	4	5.5	7.6	12.1	15.1	...	...

At the moment, we are still investigating the changes which occur in the trabeculum by varying the depth of the anterior chamber, but we may already state that the rate of outflow will be considered significant only for a given depth of the anterior chamber.

4. *Wide-Angle Glaucoma* (Case 11).

On Feb. 1, 1955, we perfused, 20 minutes after death, the right, and remaining, eye of a woman aged 77 who died of a cancer of the urinary bladder, and we obtained for C a value of 0.05 cu. mm. and for R a value of 20. These values are comparable to those obtained by clinical tonography in cases of wide-angle glaucoma. After fixation, the macroscopic and histopathologic examination of the optic nerve head of the perfused eye showed an obvious excavation (Fig. 9). Afterward we were able to obtain the clinical history of this patient, which is as follows:

On May 19, 1945, vision in each eye was 10/10. On Feb. 12, 1947, the left eye was affected by thrombosis of the central retinal vein, and a fundus examination of the right eye revealed a pale disc, Gunn's sign, and senile macular degeneration.

On Nov. 14, 1947, hemorrhagic glaucoma developed in the left eye, so that an enucleation became necessary. On Sept. 15, 1950, vision in the right eye was still 10/10, but the disc was grayish and excavated, the ocular tension was 30 mm. Hg (Schiøtz), and the visual field (Goldmann, test 2/4) concentrically narrowed to 10 to 12 degrees. The diagnosis of wide-angle glaucoma simplex was

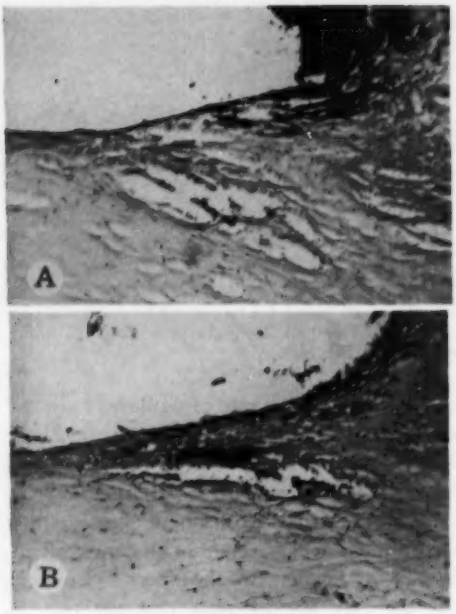


Fig. 10.—Hematoxylin-eosin stain (obj. 16 mm.; ocul. 8 ×). See text.

obvious. On March 4, 1953, vision was only 1/10 and the ocular tension 26 mm. Hg (Schiøtz).

On Jan. 15, 1955, the patient was accepted in the clinic of urology for urinary bladder carcinoma, and she died on Feb. 1, 1955.

The increase of resistance to outflow, demonstrated clearly by the perfusion test (C=0.05 cu. mm.), was caused by anatomical alterations at the level of the scleral trabeculum. First, perfused India ink appeared only after a considerable time, very sluggishly, and in only one segment of the limbal area, and to a very limited extent at the limbus.

Histological examination (Fig. 10*A* and *B*) gave the following findings:

1. At the level of the iris and ciliary body the same diffusion picture was found as in normal cases.

2. At one side of the eye no ink had entered the trabeculum; at the other side only a small amount of ink was seen between the enlarged lamellae.

3. The scleral trabeculum, moreover, presented evident anatomical alterations, more especially a narrowing of the interlamellar spaces.

Figure 11*A* and *B* permits a comparison of our case of glaucoma and a normal case.

These observations produce formal evidence that in glaucoma simplex it is the anatomical lesions of the scleral trabeculum that offer the obstacle to the outflow.

In the histological sections of Cases 7 and 8, in which perfusion gave for each eye a value for C of 0.12 cu. mm. and a value for R of 8.3, analogous alterations, but less pronounced, were detected at the level of the trabeculum (Fig. 12).

Nevertheless, the optic disc was not excavated.

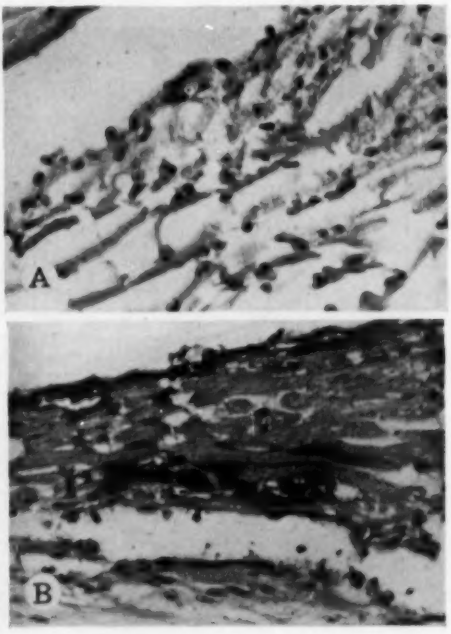
5. *Glaucoma Secondary to Rubeosis Iridis* (Case 63).

A man aged 87 15 years before had incurred a contusion of the left eye. One year later vision of this eye decreased progressively to complete blindness.

The patient was examined for the first time on April 1, 1955. He complained of severe pain in the left eye, starting nearly six days before. The right eye was completely normal. Tonography gave a value of 0.23 cu. mm. for C and 4.3 for R, ocular tension being 15 mm. Hg (Schiøtz).

The left eye showed pronounced ciliary injection, corneal edema, atrophic iris with rubeosis, nearly complete pupillary seclusion with mydriasis and areflexia, a depth of the anterior chamber of 2.5 mm.,

Fig. 11.—Hematoxylin-eosin stain (obj. 4 mm.; ocul. 8 ×). See text.



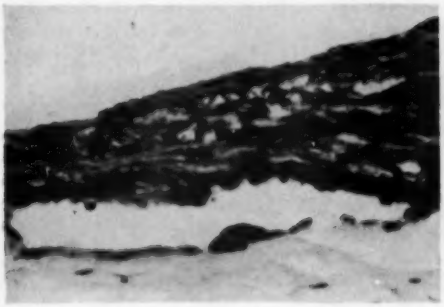


Fig. 12.—Hematoxylin-eosin stain (obj. 4 mm.; ocul. 8 ×). See text.

complete cataract, and an ocular tension of 40 mm. Hg (Schiøtz). Tonography gave for *C* a value of 0.08 cu. mm. and for *R* a value of 12.

On April 2, diathermal perforations (12) were placed in front of the insertion of the external rectus muscle. On the next day the eye was more congested and the ocular tension was 60 mm. Hg (Schiøtz).

On April 4, the tension fell to 40 mm. Hg and on April 6, to 30 mm. Hg. At this time the corneal edema had disappeared, but hyphema persisted.

The tension increased again and reached 48 mm. Hg on April 12. Another 12 diathermal perforations, this time in front of the insertion of the internal rectus muscle, were performed. On April 14, the tension was 23 mm. Hg; on April 15, it was 16 mm. Hg, and April 21, it was 8 mm. Hg.

At that time the anterior chamber had deepened. Tonography on April 20 gave 0.15 cu. mm. for *C* and 6.6 for *R* (Fig. 13).

Later, precipitates on Descemet's membrane and a slight hypopyon appeared, necessitating the enucleation of the eye.

Perfusion of this eye, in which the depth of the anterior chamber was 5 mm., gave values for *C* of 0.19 cu. mm. and for *R* of 5.3; these values are well in agreement with those obtained by the second tonography, performed with a deep anterior chamber (*C*=0.15 cu. mm. and *R*=6.6).

In order to obtain the same depth of anterior chamber as existed at the time of our first tonography (2.5 mm.), we changed the depth of the anterior chamber.

Under these conditions, the perfusion gave 0.07 cu. mm. for *C* and 14.5 for *R*, values similar to those obtained by tonography (*C*=0.08 cu. mm. and *R*=12) (Fig. 14).

These various observations permit us the following conclusions:

1. Even in pathological cases, clinical tonography and experimental perfusion may give similar results.

2. There exists a relation between rate of outflow and depth of the anterior chamber.

3. Probably the clinical tonography values depend also on the depth of the anterior chamber.

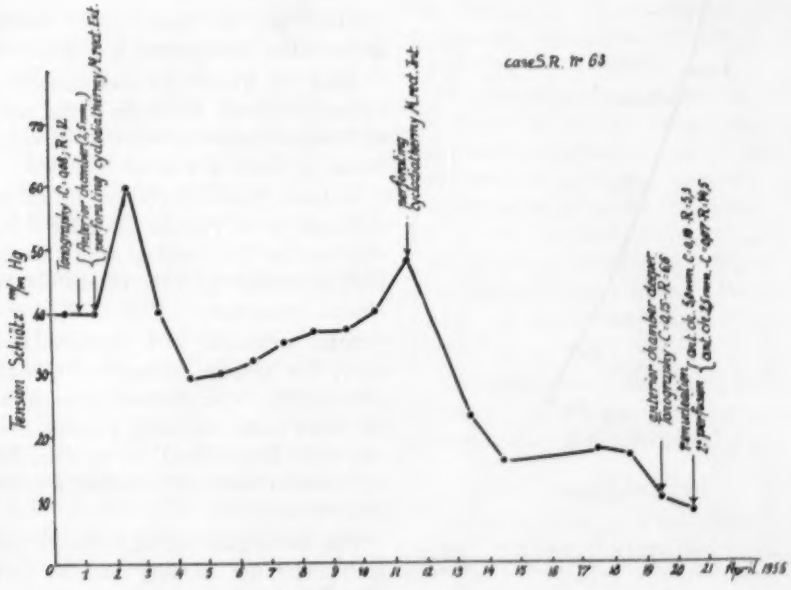


Figure 13

4. The decrease in production of aqueous humor through the cyclodiathermy deepens the anterior chamber, as has been proved by the researches of R. Weekers.

In the histological examination of this case of secondary glaucoma after perfusion with India ink, very little ink was found in the ciliary body and iris stroma (Fig. 15), but very little had penetrated into the scleral trabeculum either; in the anterior chamber, however, large masses of India ink were seen.

Schlemm's canal was not normal. At its level could be seen a vein filled with blood. Very small capillaries penetrated even into the trabecular tissue.

Around the vessels a slight fibroblastic proliferation with edema was found; these new vessels and the tissue reaction pushed the trabeculum toward the anterior chamber, narrowing its spaces by compression. These alterations may well explain the increase of the resistance to the outflow.

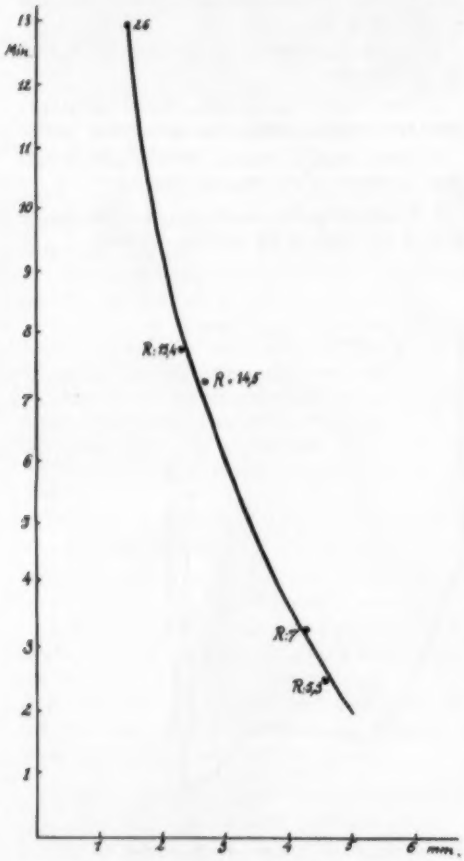


Figure 14

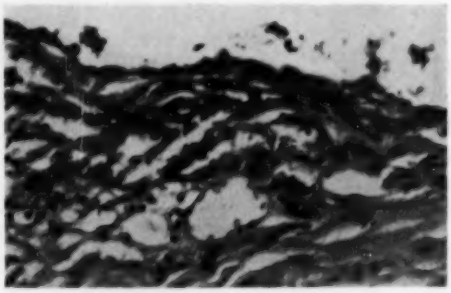


Fig. 15.—Hematoxylin-eosin stain (obj. 4 mm.; ocul. 8 ×). See text.

SUMMARY

Rabbit Eyes.—Perfusion of 62 rabbit eyes gave an average value for *C* of 0.21 cu. mm. and for *R* of 4.7. After treatment with hyaluronidase the increase of *C* was 40% to 50%.

The histological examination of rabbit eyes perfused with India ink showed that the ink flowed only out through the trabeculum and that after treatment with hyaluronidase the infiltration of the trabeculum by India ink was much more pronounced.

These facts are confirmed by microradiograms taken after perfusion with Thorotrast.

After the trabeculum was scraped over a circumference of 90 degrees, the resistance to outflow decreased considerably; after perilimbal incisions it was not modified.

Human Eyes.—Perfusion of 67 human eyes gave as an average value for *C* 0.25 cu. mm. and for *R*, 4, findings which are in complete agreement with the results obtained by clinical tonography.

After treatment with hyaluronidase (24 eyes) the average increase of *C* was only 25% to 30%. The effect of hyaluronidase, on the other hand, was very variable from one case to another; indeed, the maximal decrease of resistance which we obtained was between 5% and 66%.

The histological sections of eyes perfused with India ink showed that the perfusion fluid leaves the anterior chamber through the

scleral trabeculum, but no appreciable difference was found before and after treatment with hyaluronidase.

The microradiograms performed after perfusion with Thorotrast showed a marked difference.

Depth of Anterior Chamber.—The degree of depth of the anterior chamber has a great influence on the rate of outflow: The latter is higher when the anterior chamber is deeper and decreases when the anterior chamber is shallower; this phenomenon is reversible. For a given determined depth, on the other hand, we always obtained the same rate of outflow.

Wide-Angle Glaucoma.—Perfusion of the eye, enucleated 20 minutes after death, gave for C and R the values of 0.05 cu. mm. and 20, respectively, showing a very high resistance to outflow.

The histological examination, after perfusion with India ink, demonstrated a nearly complete absence of ink in the trabeculum; it showed, moreover, an obvious narrowing of the interlamellar spaces.

Secondary Glaucoma.—In a case of secondary glaucoma due to rubeosis iridis, a first tonographic study, done when the ocular tension was 40 mm. Hg and the depth of the anterior chamber 2.5 mm., gave 0.08 cu. mm. for C and 12 for R. A second tonography, done at a moment when the tension was 8 mm. Hg and the anterior chamber deeper, gave 0.15 cu. mm. for C and 6.6 for R.

The perfusion of the enucleated eye, with a depth of the anterior chamber of 5 mm., gave 0.19 cu. mm. for C and 5.3 for R, values which are consistent with the results obtained by the last tonography.

The perfusion of the same eye, in which the depth of the anterior chamber was brought to 2.5 mm., gave 0.07 cu. mm. for C and 14.5 for R, values which are consistent with the results of the former tonography.

These facts demonstrate, again, the importance of the depth of the anterior chamber.

The histological examination after perfusion with India ink showed that a small amount of ink penetrated into the trabeculum. On the other hand, in the area of scleral trabeculum and Schlemm's canal, evident histopathological lesions were present, a finding which may explain the increase in resistance.

CONCLUSIONS

The rate of outflow obtained by perfusion of human eyes is the same as that obtained by clinical tonography (C=0.25 cu. mm. and R=4).

Because the experimental conditions are not influenced by any circulatory or nervous changes, it is clear that the outflow of the perfusion fluid depends only upon anatomical conditions.

The addition of hyaluronidase to the perfusion fluid has a much slighter and more variable effect on the outflow in human eyes than in rabbit eyes.

The rate of outflow is directly proportional to the depth of the anterior chamber, and the factor of the chamber depth should be considered as much in the clinical tonography as in the experimental perfusion value.

In a case of wide-angle glaucoma, the perfusion study, as well as the tonographic measurement, shows an increased resistance to outflow (C=0.05 cu. mm. and R=20), while the histological examination shows at the trabeculum obvious lesions, which offer the obstacle to the outflow.

In a case of glaucoma secondary to rubeosis iridis, the clinical tonography and the experimental perfusion have, again, given results well in agreement, and have demonstrated the importance of the anterior chamber depth (depth=2.5 mm.: tonography, C=0.08, and perfusion, C=0.07; tonography with deep anterior chamber: C=0.15; perfusion with an anterior chamber 5 mm. deep, C=0.19).

The histological examination of this case, moreover, shows important alterations in the tissues around the iridocorneal angle.

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Human Chorioretinal Burns from Atomic Fireballs

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More brilliant than the sun or any other natural light source visible on earth is the man-made fireball of the atomic and hydrogen detonations. Depending on the intensity, light sources of such extreme brightness may have both temporary glare and burning effects. The glare effects from nuclear explosions are similar to those experienced when looking directly at the sun. The permanent lesions from the fireballs have a parallel in the chorioretinal burns described as eclipse blindness.* For generations smoked glass has been used to prevent eclipse burns. Very dense filters † have been routinely and successfully employed to protect the eyes of observers of experimental atomic detonations.

On a theoretical basis [2] it had been predicted that damage to the unprotected retina would occur at distances greater than any known biological effect from the fireball of atomic detonations. To test this prediction, extensive experiments with rabbits have been performed and have demonstrated that chorioretinal burns may occur from exposure to atomic bombs at distances up to 42.5 miles.‡ The literature reveals no report of such a burn except for a single case of bilateral central scotoma incurred in the Hiroshima atomic explosion.[4]

The lesions found in the rabbits were characteristically round and sharply circumscribed, consisting of a central and a peripheral zone. In lesions produced at short distances from the fireball a central hole through the retina and choroid was seen, exposing the sclera. The hole was surrounded by an elevated margin and gray halo. Hemorrhages were frequently found. In lesions produced at medium distances, instead of a central hole, there was a yellowish-white coagulated area in the retina and choroid. The surrounding dirty-gray halo diminished in size. At great distances the lesion was represented only by a circumscribed pigmentation, which on histologic examination revealed a coagulation necrosis of the retina.

The chorioretinal damage occurred at much greater distances from atomic flashes than skin burns are known to occur. This is due to the focusing effect of the optical system of the eye and to the pigment distribution in the tissues. While the irradiation of the pupil (as that of the skin) diminishes with the square of the distance, the area of the retinal image diminishes equally with the square of the distance, up to distances at which the image is no longer resolved. Therefore, up to such distances, the energy per unit area incident on the retina remains the same except for attenuation by the air. This is similar to the constancy of apparent brightness of an object when viewed from different distances.

The extent of the chorioretinal injury depends on the heat generated in the pigmentary layers. Since these layers are very thin, the energy is absorbed in a very small volume. Consequently, high temperatures are reached very rapidly. Close to the detonation this temperature should theoretically be

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* Byrnes and others.[1] This article contains an extensive list of papers concerning eclipse blindness.

† Filter density 4.5.

‡ References 1 and 3.

higher than the boiling point of water, causing a water-vapor explosion. Ophthalmoscopic and histologic examination of the rabbits in the above-mentioned experiment suggested that such explosions occurred.

Eclipse blindness occurs only if the sun is fixated voluntarily and the blink reflex is consciously suppressed. However, the human blink reflex, occurring at an average within 0.1 second, is not fast enough to prevent damage from atomic detonations. The latter has a peak of emission before 0.01 second. During this early phase, the fireball of a nominal weapon reaches brightness up to 100 times that of the sun. The area of the pupil determines the irradiation of the retina; therefore, the wide night pupil makes chorioretinal burns more probable at night. A detailed discussion of the physical factors was given in a previous paper.[1]

With increasing amounts of visible and infrared radiation striking the retina, the following sequence of events can be demonstrated. Relatively small amounts of visible radiation in excess of that to which we are adapted cause glare. This is a temporary effect. Greater amounts of visible radiation cause after-images, which may last for seconds, minutes, or hours. Temporary or permanent scotomata without ophthalmoscopic changes are caused by even stronger visible or infrared radiation. Transient localized retinal edema without sequelae can accompany these scotomata. Excessive degrees of visible and infrared irradiation cause permanent chorioretinal burns, with resultant scotoma and possibly retinal detachment. Burns of the macula and optic nerve obviously are disastrous. Various degrees of thermal irradiation damage from atomic detonations are demonstrated in the following cases.

REPORT OF CASES

CASE 1.§—A 43-year-old Air Force photography officer viewed in daylight the latter part of an atomic flash through the optical view finder of a C-6 type Speed Graphic camera with his left eye, through an open window of an aircraft at 6 miles from the detonation of a small atomic weapon. His unshielded, right eye viewed the detonation also. He had performed a similar procedure on several previous occasions and had experienced no visual disturbance. However, he stated that he had not previously viewed the fireball at such an early time after detonation. He experienced an immediate marked dazzle effect and shortly thereafter blurring, haziness, photophobia, and "shimmering." He did not recall seeing an after-image. In the evening of the same day extreme photophobia and visual disturbance forced him to stop driving and remain parked until dawn. He saw halos around street lights. Twenty-four hours after the detonation his visual acuity was found to be 20/30 O. D. and 20/50 O. S. Visual disturbances were less marked 48 hours after exposure. His visual acuity was then 20/15 O. D. and 20/15 O. S. His lids were slightly swollen, and his conjunctivae were markedly injected. Ophthalmoscopic examination of the right eye revealed a normal fundus. In the left eye a minimal diminution of the foveal reflex was observed; otherwise the left fundus was normal (Fig. 1). His peripheral visual fields were normal for 3/330 white. The central visual fields, taken with 1/1000 white, were concentrically constricted in both eyes. A relative scotoma was found in the nasal half of the left paracentral field (Fig. 2).

CASE 2.—This 35-year-old pilot viewed an atomic explosion from a distance of 5 miles with his right eye through an aircraft window. His left eye was covered. He was blinded for 15 seconds, and after 20 to 25 seconds he was able to see aircraft instruments only hazily. This lasted at least 8 to 10 minutes. Seven months after the explosion he had visual acuity of 20/15 in each eye. A paracentral scotoma was found in the upper temporal quadrant of his right visual field. There was an absolute scotoma of 2-degree diameter for 0.5/1000 white and, surrounding it, a relative scotoma for 3/1000 white of about 5-degree diameter (Fig. 3). Careful

§ This patient was referred to us by Col. Clinton Maupin (MC), U. S. Army.

Fig. 1 (Case 1).—Left fundus photograph after atomic flash. The reflection and dark spot in the center of this and of the following photographs are artifacts of the retinal camera.

Fig. 5 (Case 3).—Chorioretinal lesion in left eye following atomic flash. *A*, drawing 5 days after exposures; *B*, drawing 8 days after exposure; *C*, drawing 12 days after exposure; *D*, photograph 30 days after exposure, lesion indicated by arrows; *E*, drawing 100 days after exposure.

Fig. 6 (Case 4).—Retinal photograph of bilateral chorioretinal burn two months after exposure to atomic flash. Arrows indicate the lesions. *A*, right eye; *B*, left eye.

Fig. 9 (Case 5).—Fundus photograph of left eye exposed to atomic flash three months after exposure. Lesion indicated by arrow.

Fig. 11 (Case 6).—Fundus photograph of left eye six weeks after exposure to atomic flash.

Fig. 1

Fig. 5A

Fig. 5B

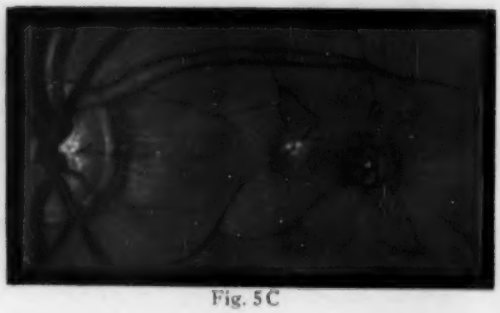

Fig. 5C

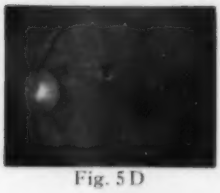

Fig. 5D

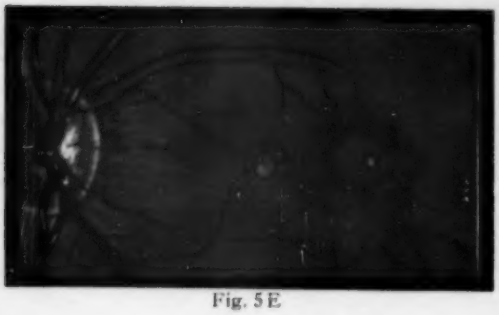

Fig. 5E

Fig. 6A

Fig. 6B

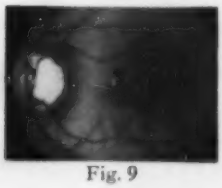

Fig. 9

Fig. 11

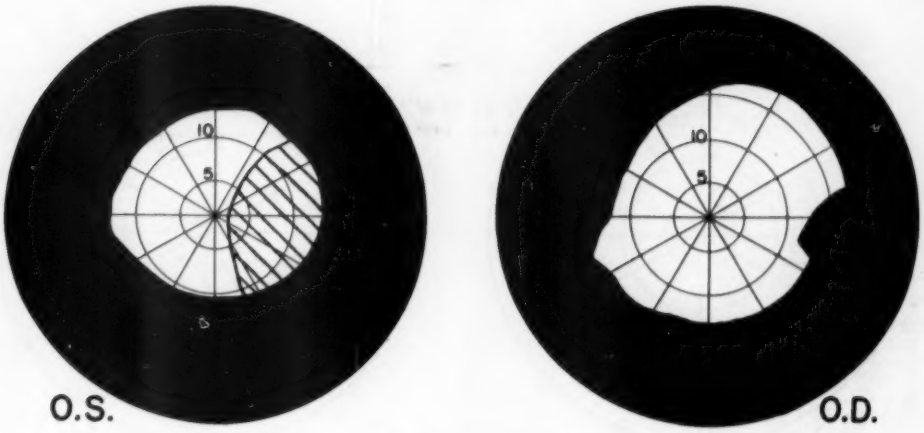

Fig. 2 (Case 1).—Central visual fields for 1/1000 white following exposure to atomic flash. Concentric constriction in each eye. Hatched area indicates relative scotoma in the left nasal paracentral area.

ophthalmoscopic examination revealed no chorioretinal lesion.

Case 3.‖—This 27-year-old pilot viewed an atomic explosion from a distance of 10 miles with his left eye without protective filters. The observation began 50 msec. after detonation. Subjective visual difficulties persisted for no more than five minutes. An examination one month prior to the exposure revealed visual acuity of 20/15 in each eye, no field defects for 2/1000 white, and normal fundi. Five days after the exposure, his visual acuity was 20/15 in each eye; however, a paracentral scotoma was found in the left eye of about 2-degree diameter (Fig. 4). He was aware of this scotoma when closing the right and blinking the left eye. Visual acuity and visual fields remained unchanged on all subsequent examinations.

Ophthalmoscopically, a blanched area fairly well demarcated (approximately 1/10 disc diameter) was found nasal to the fovea and immediately adjacent to that branch of the inferior temporal artery which leads to the perimacular area (Fig. 5*A*). The lesion was slightly oval, with the long axis vertical. In the area of the lesion, the branch of the

‖ Certain examinations of this case were performed by Lieut. Col. Jack H. Bristow (MC), U. S. A. F.; Lieut. Col. John R. Grunwell Jr. (MC), U. S. A. F., and Capt. Gustav C. Bahn (MC), U. S. A. F.

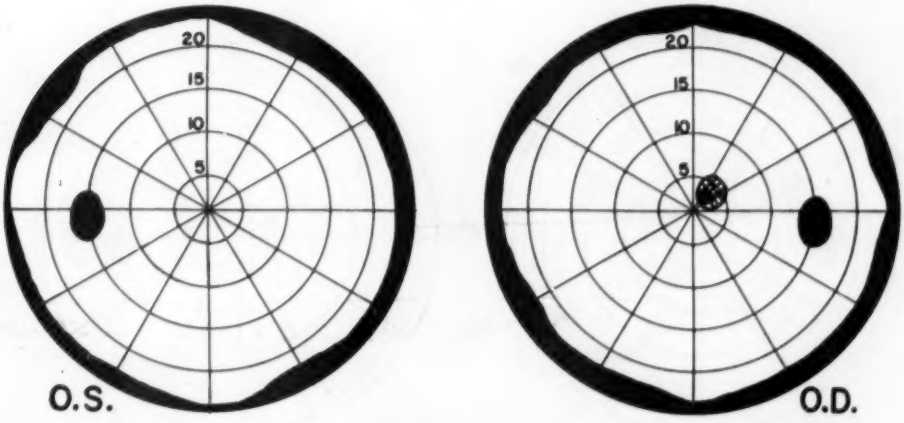

Fig. 3. (Case 2).—Central visual fields for 1/1000 white one month following exposure to atomic flash. Solid black indicates absolute scotoma for 3/1000 white. Cross hatching indicates absolute scotoma for 0.5/1000 white.

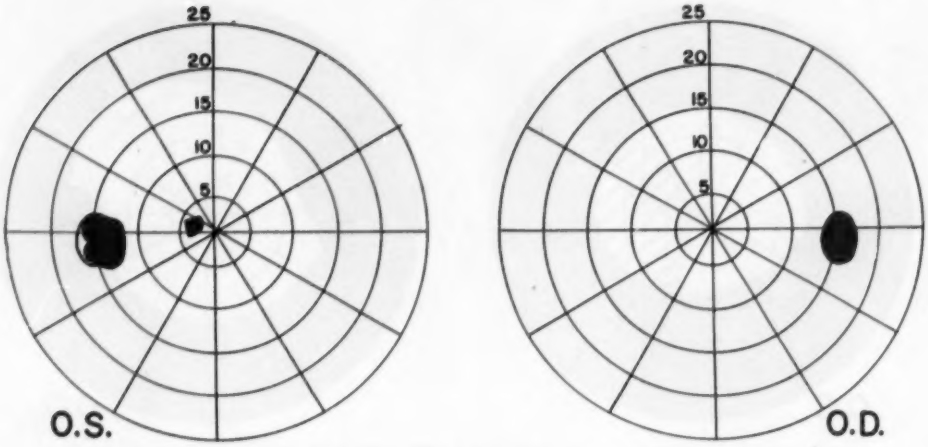

Fig. 4 (Case 3).—Central visual fields for 2/1000 white five days after exposure to atomic flash. Black area indicates paracentral scotoma in the left eye.

inferior temporal artery assumed a bright reflex and apparently was devoid of blood distally. The blanched area was surrounded by a small zone of retinal edema. On the eighth day the lesion was slightly more sharply defined and edema had decreased (Fig. 5*B*). At 12 days the retinal edema was further diminished (Fig. 5*C*). After one month the retinal edema had disappeared and pigment was found deposited in the lesion (Fig. 5*D*). The ophthalmoscopic findings were unchanged 100 days after exposure (Fig. 5*E*).

Case 4.—This 19-year-old airman viewed with both eyes a detonation of an atomic bomb from a distance of 10 miles. No eye protection was worn. He blinked immediately and turned away. No subjective visual disturbances were noted. A routine examination two months after the exposure revealed sharply demarcated bilateral chorioretinal lesions about 1.5 × 1 mm. in size. The lesion in the right eye was located between the disc and the macula about 2 mm. below a line connecting them (Fig. 6*A*). The lesion of the left eye was found astride a retinal vein about 1½ disc diameter lateral to and ½ disc diameter below the macula (Fig. 6*B*). The lesions were identical in appearance—oval with slightly depigmented margins. There was no edema and no deviation from the level of the surrounding retina. Visual acuity was 20/25 in each eye. Visual fields revealed symmetric scotomata corresponding to the lesions (Fig. 7). These scotomata were about 1 degree in diameter for 5/1000 white, with the surrounding scotomata of about 5-degree diameter

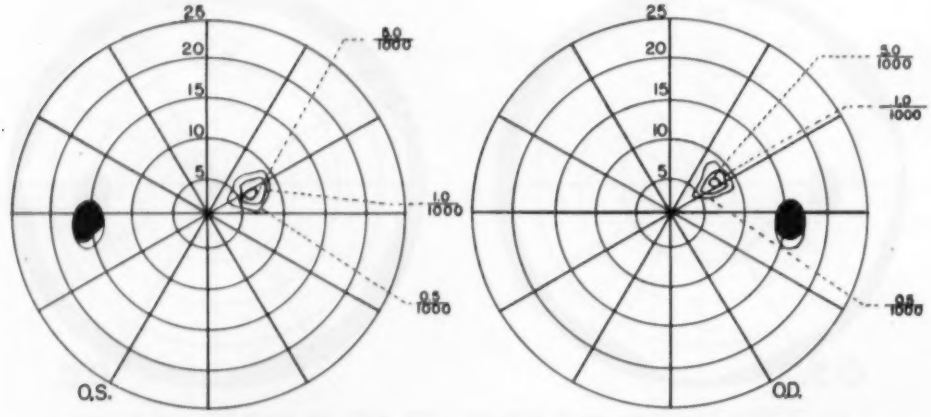

Fig. 7 (Case 4).—Central visual fields two months after atomic flash exposure. Scotomata in each eye plotted with 5/1000, 1/1000, and 0.5/1000 white.

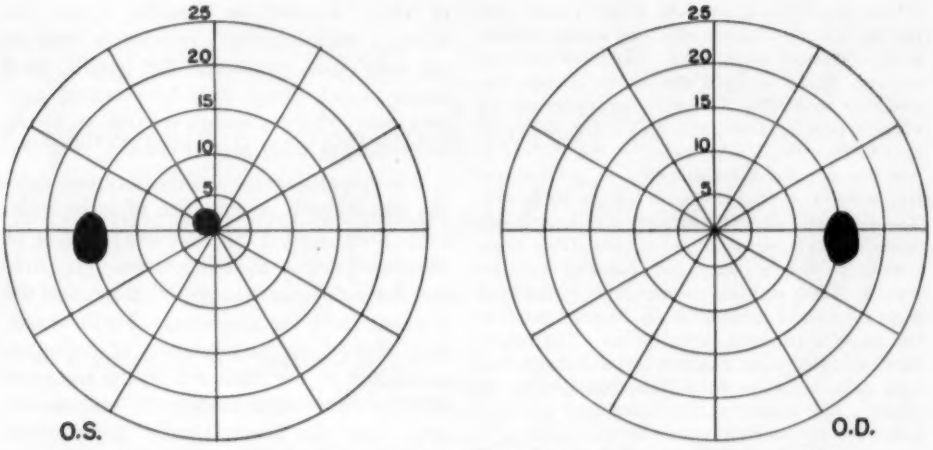

Fig. 8 (Case 5).—Central visual fields (1/1000 white) one month following exposure to atomic flash. Paracentral scotoma in the left eye indicated by solid black.

for 0.5/1000. The patient was examined repeatedly during the following 18 months. No change was found in the ophthalmoscopic appearance, visual fields, or visual acuity.

Case 5.—This 20-year-old officer viewed the detonation of an atomic bomb from a distance of 7 miles. His right eye was covered; his left eye was protected with a filter transmitting about 3% of the visible light. He made a conscious effort to keep his left eye open and was probably exposed for one second from the beginning of the flash. Examination two months prior to the exposure gave normal findings except for moderate myopia. Immediately after exposure this officer noted a central blind spot in the left eye. His visual acuity one month after exposure was 20/20 corrected in each eye. Visual field examination revealed a paracentral scotoma of about 4-degree diameter at the fixation point for 1/1000 white (Fig. 8). Ophthalmoscopy of the left eye showed an elliptical lesion of about 1/6 disc diameter immediately below the macula. The margins of the lesion were elevated and yellowish-pink. In the center of the lesion dirty-gray sclera was visible, with small pigment deposits. There were no hemorrhages or exudates. There was slight retinal edema about the lesion. On his last examination, three months after exposure, a positive scotoma was still present; his visual acuity and visual fields were unchanged. The chorioretinal lesion appeared as described; however, the edema had disappeared (Fig. 9).

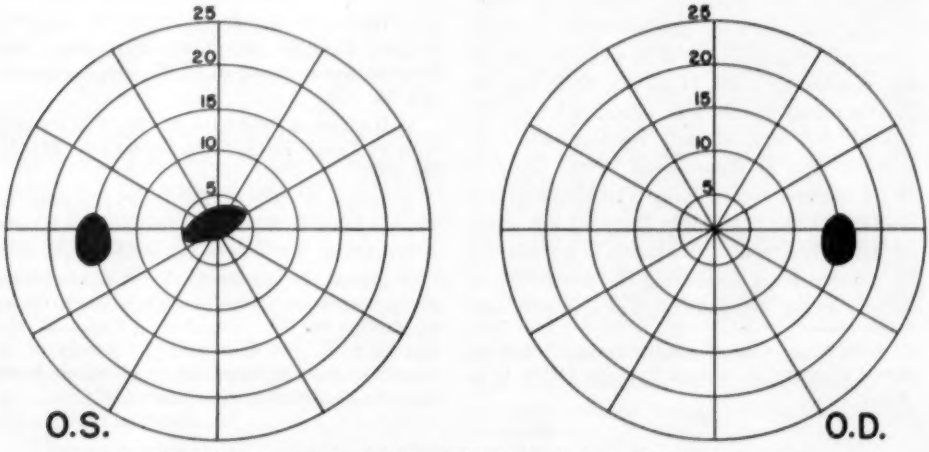

Fig. 10 (Case 6).—Central visual fields (1/1000 white) six weeks after exposure to atomic flash. Black area indicates absolute central scotoma.

CASE 6.¶—This 22-year-old officer viewed with his left eye the detonation of an atomic weapon from a distance of 2 miles. His right eye was covered. Visual acuity of the left eye dropped immediately to 20/200. Six weeks after exposure the visual acuity, right eye, was 20/20; that of the left eye, 20/70. Visual field studies of the left eye at that time revealed a horizontally oval absolute central scotoma of about 5 by 8 degrees (Fig. 10). The peripheral part of the lesion was located just below the line bisecting the macula. The upper convex portion of the lesion extended into the macula. There was neovascularization, particularly from the inferior temporal retinal artery; less from the superior temporal retinal artery. The central portion of the lesion was a brownish color (probably hemorrhage) with a pigmented spot in the center. The surface of the lesion was generally below the surrounding retina. Retinal edema completely surrounded the lesion. Radiating elevated retinal folds extended out from the lesion to the periphery (Fig. 11).

COMMENT

The ophthalmoscopic appearance in the human cases reported above is quite similar to the picture seen in eclipse blindness and in the rabbit experiments with nuclear devices. Case 1 is that of a relatively recent exposure, and the patient has been examined only once. The negative ophthalmoscopic findings and the presence of only a relative scotoma suggest that in this case restoration of visual function is possible. Despite the lack of visible fundus injury in Case 2, it is probable that the scotoma is permanent because it has persisted more than seven months since the exposure. From the ophthalmoscopic examination it is evident that in the remaining cases (Cases 3, 4, 5, and 6) chorioretinal tissue was destroyed and replaced by scar tissue; consequently, we assume that in these areas visual function is permanently destroyed. The shape of the lesion in Case 6 strongly suggests the shape of the early fireball. This lesion is surrounded by tension lines, indicating the possibility of future retinal detachment. Thus, impairment of visual function is possible beyond the primary retinal lesion. Similarly, a burn on the optic disc, papillomacular bundle, or a major vessel would have far-reaching consequences. Macular lesions are serious, owing to the loss of acute central vision.

The size and severity of chorioretinal damage depend on a combination of several factors. They depend on the energy output of the atomic device, the temperature of the fireball during observation, the distance, and the attenuation by the atmosphere. Furthermore, they depend on the duration of exposure, as limited by the blink reflex, the transparency of the ocular media, the size of the pupil, and the absorption by the pigment epithelium. Since by night the area of the pupil can be 64 times that in bright daylight, it is obvious that the damage of a night-time atomic detonation is far greater.

The cases reported give further evidence that the human blink reflex is inadequate protection against the atomic flash.

¶ This case was previously examined and referred to us by Col. Milford T. Kubin (MC), U. S. Army.

SUMMARY

The history, ophthalmoscopic findings, and visual impairment in six human cases of chorioretinal burns due to atomic flash are described. The physical, anatomical, and physiological factors contributing to the production of the lesions are discussed.

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Experimental Approach to the Pathogenesis of Retrolental Fibroplasia

VII. Effect of Oxygen Exposure on the Electroretinogram in Kittens

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There is convincing evidence that exposure to oxygen is intimately related to the occurrence of retrolental fibroplasia in premature infants.* The more immediate relationship is, however, not exactly known, and many problems remain to be solved. The importance of a lowering of the environmental oxygen concentration for the development of vasoproliferating changes is an unsettled question. The study by Bedrossian and associates [2] pointed to a higher incidence of the disease in infants suddenly withdrawn from high oxygen concentrations as compared with the occurrence in children slowly weaned. On the other hand, it was pointed out in the preliminary report of the cooperative study [3] that the prolongation of the stay of the infant in oxygen to permit slow weaning might increase the risk of developing the disease. Another problem concerns the question as to whether external factors other than oxygen exposure influence the pathological vascularization of the retina. In recent animal experiments [1] a process of gradual lowering of the high oxygen environment did not prevent the oxygen-induced disease in mice. In another study, the importance of the nutritive state of the animals was explored as regards the normal and pathological outgrowth of retinal vessels in oxygen-exposed mice and control animals.[4]

With the growing conviction that oxygen exposure, even of relatively short duration, is the main factor in producing the disease in premature infants, a restrictive utilization of oxygen therapy has been generally adopted. In order to gain more information about the pathogenesis of the disease, animal experimentation is necessary, and conclusions thus drawn seem valid, as the pathology of the oxygen-induced disease in animals of certain species is closely similar to the early pathology of the disease in premature infants.†

Two different stages of the disease in animals have been well recognized: one, the vaso-obliterative phase, followed by a vasoproliferative phase,† the latter usually occurring on transfer from high to low oxygen atmosphere.‡ In premature infants an initial vasoconstriction has also been observed,[8] but this phase is usually not included in the description of the ophthalmoscopic stages of the disease.[9] From these observations a hypothesis has been advanced that the initial vasoconstrictive and vaso-obliterative phenomena cause a paradoxical retinal hypoxia, possibly aggravated when the environmental oxygen concentration is lowered.

Although seemingly plausible, this hypothesis has not been proved. One of the basic questions seems to be whether or not signs of disturbed metabolism or retinal function can be demonstrated during continuous oxygen

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* References cited are by Gyllensten and Hellström.[1]

† References 5 to 7.

‡ References 6 and 7.

exposure. From Ashton's experiments § with newborn kittens, it is known that a partly irreversible vaso-obliteration of retinal vessels occurs during oxygen exposure. It does not seem likely that such an irreversible obliteration is merely compensatory as a response to the increased oxygenation of the blood.

The present study was undertaken with the object of studying the immature retina in animals during continuous oxygen exposure from a functional point of view. Electrophysiological methods applied to the retina must be considered the best sources of objective information concerning the general state of retinal function under normal and abnormal conditions.[11] The electroretinogram, that is, the retinal response to illumination, has generally been studied more closely than, for instance, the steady potential differences, and has thus been used as a suitable and easily measurable phenomenon, reflecting the condition of the retina.

MATERIAL AND METHODS

Kittens were used as experimental animals, for several reasons. According to Michaelson,[12] there is a great similarity between the retinal circulation of cat and that of man, both having a superficial capillary net lying in the nerve fiber layer and a deep capillary net lying in the outer and inner aspects of the inner nuclear layer. The process of retinal vascularization is completed during the first three weeks of postnatal life in the cat. In man the vessels reach the ora serrata in the eighth month of intrauterine life. Thus, the stage of retinal vascularization in a kitten from birth to 3 weeks of life can be compared with that of newborn children with different degrees of prematurity. Furthermore, oxygen-induced changes of the retinal vessels in the kitten, closely similar to the early pathology of retrolental fibroplasia, have successfully been produced.‖ Another reason for using kittens as experimental animals was the fact that the development and pattern of the electroretinogram in normal kittens have recently been studied.¶

Methods for Oxygen Exposure.—Short Exposure: Oxygen exposure for approximately 12 hours was accomplished in the following way in order to secure continued exposure during the recording of the electroretinogram. The animals were anesthetized with pentobarbital (Nembutal) intraperitoneally at a dosage of 0.25 mg. per 100 gm. of body weight. Tracheotomy was performed, and a T-shaped glass cannula was used, the vertical stem of the T having a length of about 2 cm. and a diameter adjusted to the width of the trachea, where it was inserted. Through the horizontal portion of the cannula, which had a greater diameter, a steady flow of oxygen or a mixture of oxygen and nitrogen was led. Entering the free end of the cannula, a small polyethylene tube could be introduced into the trachea and a specimen withdrawn to be analyzed with a Beckman oxygen analyzer. The gas flow was kept moist by bubbling through water.

Long Exposure: Animals to be exposed to high oxygen concentrations for a longer period were kept with their mothers in especially constructed incubators. These had a volume of approximately 190 liters and were provided with a gas inlet tube at the bottom of one side and with two outlet tubes, one at the bottom and one at the top of the opposite side, for the collection of samples for oxygen analysis. The incubators were also equipped with air-tight valve chambers for the feeding and handling of the animals and a sawdust tray, below which self-indicating soda lime was spread to absorb CO_2. The mothers were taken out three to four hours daily. If the incubators had to be cleaned, the kittens were placed during the procedure in another incubator with the same atmosphere. The cats were fed with fresh fish and milk. The flow of the oxygen-nitrogen mixture was 2.5 liters per minute. The oxygen concentrations were measured with a Beckman oxygen analyzer several times a day. The range of the fluctuations of the oxygen concentrations was ±5 vol. %. CO_2 was not measured. The humidity was close to 100%; the temperature varied between 20 and 25 C.

Several animals were lost from feline panleucopenia, which rendered following the results difficult, as most of the kittens died at an age of 6 to 8 weeks. The weight gain of the kittens raised in the incubators was as a rule slightly below normal.

When a record of the electroretinogram (ERG) in long-exposed animals was to be made, a tracheotomy was performed, with the insertion of a cannula as described previously, and a flow of oxygen was then administered at the same concentration as that in the incubator. The procedure necessitated a stay in air for a period of less than 10 minutes; otherwise the exposure to oxygen was continuous until the recording of the ERG.

Recording Technique.—Before the recording of the ERG the pupils were dilated with a 1% atropine solution and the cornea anesthetized with a 1% solution of tetracaine (Pontocaine) hydrochloride. The technique of the recording was the same as that used by Karpe.[13] As active electrode, contact glasses with chlorinated silver rods were used. The

§ References 6 and 10.

‖References 5 and 6.

¶ Zetterström, B., to be published.

indifferent electrode was attached to one ear. The time allowed for dark adaptation was five minutes. Both eyes were examined as a rule. The intensity of the stimulating light was 80 and 800 luxes, the latter giving a maximal response, as judged by the size of the b-wave.# Only the first portion of the ERG, including the a- and b-waves, was studied. The ERG following the 800-lux stimulus was analyzed as to latent periods and amplitudes of a- and b-waves and the duration of the b-wave. The respiratory rate was checked as indicating the depth of narcosis, and records from an animal with a respiratory rate of less than 20 were discarded.

RESULTS

According to Zetterström,# the ERG is entirely absent in kittens during the first five days of life. Between the 6th and the 10th day the first sign of a small b-potential appears, the wave increasing in amplitude with advancing age and reaching adult levels at 9 to 10 weeks of age. The a-wave is usually absent during the first weeks and never dominates the ERG with greater amplitude than that of the b-wave in case the animal is not too deeply anesthetized. Other changes also occur in the ERG with advancing age; the duration of the b-wave decreases, with steeper ascending and descending parts of the wave.

Effect of Narcosis.—There were some difficulties in keeping the animals at the suitable level of anesthesia for as long as 12 hours. Because of this, some experiments were carried out on control animals aged 2 to 4 weeks, using varying doses of pentobarbital. The respiratory rate was normally 30 to 60 per minute and seemed fairly well correlated with the depth of the anesthesia. It was found that the ERG was influenced when the narcosis was as deep as to give a respiratory rate of 20 or less. This influence started with a decrease of the b-wave, the a-wave being relatively dominant. By degrees the b-wave entirely disappeared, and finally the ERG became extinguished. These findings are in accordance with those made by Zetterström * and by Granit [14]; in the latter investigation the effect of ether narcosis was studied.

Zetterström, B., to be published.

* Zetterström, B., to be published.

Because of this, care was taken to keep the animals in the following experiments in an anesthesia as superficial as possible, and, if at the end of a record the respiratory rate had decreased below 20, the ERG was discarded.

Effect of Short Oxygen Exposure.—In the experiments by Ashton and Cook,[10] with direct observation of the effect of oxygen on developing retinal vessels in kittens, an immediate and a delayed reaction following oxygen exposure were described. The former consisted of vasoconstriction and capillary obliteration, developing after five minutes' exposure to oxygen. After five and one-half hours the delayed effect was said to come into operation, when the vessels again constricted, and total vaso-obliteration was complete in about eight hours. This phenomenon was observed in all the kittens of a certain age.

It was thought of interest to see whether under similar experimental conditions changes occurred in the ERG. If these vascular changes occurred as regularly and extensively as described, it seemed likely that the ERG would show some alteration, indicating a circulatory disturbance. No attempt was made in the experiments to observe the retinal vessels ophthalmoscopically, as for this purpose a special technique is necessary, which impairs the physiological conditions.[10]

Both eyes of 14 animals, aged 12 to 17 days, were examined. Most of the animals were in the age group (14 days of age or less) at which the retinal vessels are considered to react with a total or severe obliteration on high concentrations of oxygen.[6] The concentration of the oxygen in the trachea was 85% to 95%; the duration of exposure, 10 to 13 hours. The results have been tabulated (Table). In this age group the ERG merely consists of a small b-wave. The amplitude of this b-wave was calculated before and after the oxygen exposure. Each figure represents the mean of five records. The only change following the oxygen exposure was small variations in the amplitude of the b-wave, which had decreased in nine eyes, increased in eight eyes, and was unchanged in

six eyes. The latent period showed only relatively small variations; a decrease following the oxygen exposure was more frequent. In no case did a negative a-wave appear. A typical case is illustrated in Figure 1. A few of the cases were again recorded one to two days after the discontinuance of oxygen, giving ERG's of similar character.

Effect of Long Oxygen Exposure.—The purpose of this part of the investigation was to study the electrophysiological reaction of the retina of kittens subjected to a maximal oxygen effect on the retinal vessels. The kittens were put into the incubator within the first 12 hours of life and kept there for 21 to 28 days, that is, for the whole period in which the retinal vessels are susceptible to oxygen.[6] The concentration was kept at the 70% level, which is a concentration giving complete vaso-obliteration.[6] This concentration did not seem to affect the general condition of the kittens, except for the slightly slower gain in weight already mentioned.

The Electroretinogram in Kittens Twelve to Seventeen Days of Age Exposed to Oxygen for Ten to Thirteen Hours *

Age, Days	No. of Hours in Oxygen	Amplitude of the b-Wave		
			Before Oxygen	After Oxygen
12	12½	R	0.05	0.07
		L	....	....
13	10	R	0.07	0.07
		L	....	....
13	12	R	0.06	0.06
		L	0.10	0.06
13	12	R	0.09	0.08
		L	....	....
13	13	R	0.11	0.08
		L	0.12	0.08
14	12	R	0.13	0.09
		L	0.15	0.10
14	12½	R	0.09	0.11
		L	0.11	0.09
14	11	R	0.05	0.07
		L	0.08	0.08
14	12	R	0.05	0.05
		L	0.07	0.06
15	12	R	....	....
		L	0.07	0.07
16	13	R	0.09	0.06
		L	0.06	0.08
16	12	R	0.11	0.06
		L	0.07	0.07
16	11	R	0.05	0.08
		L	0.06	0.07
17	12	R	0.07	0.07
		L	0.07	0.10

* Light stimulus, 800 luxes.

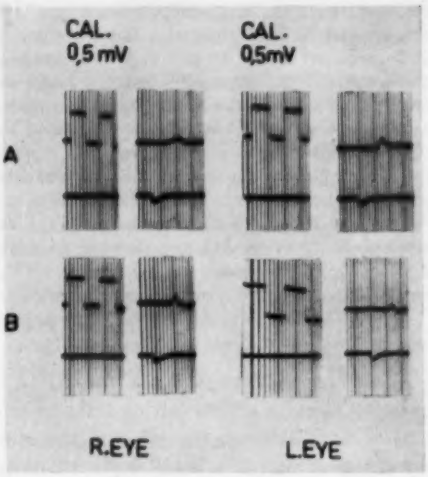


Fig. 1.—ERG in a 14-day-old kitten. Light stimulus 800 luxes. *A*, before oxygen; *B*, after 12 hours of oxygen. On the right side a slight increase, on the left side a slight decrease, in the amplitude of the b-wave.

Nor did it appear to impair the well-being of the mothers.

The ERG was recorded on both eyes after tracheotomy; most animals were subjected to repeated examinations during the following days, some of them up to three weeks after the discontinuance of the oxygen, that is, up to an age of approximately six weeks. Eighteen animals were examined. Pathological results were encountered in high frequency. According to Karpe's classification,[13] four types of pathological responses of the ERG in man can be distinguished: (1) an ERG of subnormal size ("subnormal ERG"); (2) a more or less pure negative response ("negative ERG"); (3) no electrical response ("extinguished ERG"), and (4) an ERG of supernormal size ("supernormal ERG").

The type of pathological ERG observed in these experiments was of the negative type.† Furthermore, different degrees of negativity could be demonstrated (Fig. 2). In the most extreme cases the response consisted merely of a negative a-wave, and the b-wave was completely extinguished (complete negativ-

† In this paper the criteria for an ERG being classified as negative are not the same as those used in clinical electroretinography (Karper and Uchermann [13a]).

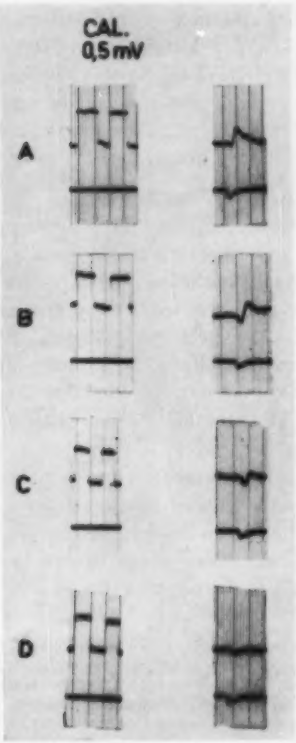


Fig. 2.—Different degrees of negativity of the ERG in kittens following a stay of 24 days in oxygen, from birth. Light stimulus 800 luxes. *A*, normal ERG, control animal; *B*, deep a-wave; *C*, dominating a-wave; *D*, complete negativity.

ity). In others a b-wave was present but had a lower amplitude than that of the a-wave (dominating a-wave). A third type consisted of an abnormally deep a-wave, followed by a normal or subnormal b-wave, but in this type the amplitude of the b-wave exceeded that of the a-wave (deep a-wave). This type was considered definitely abnormal if the amplitude of the a-wave exceeded one-third of the b-wave. Complete negativity was found in 6 eyes; a dominating a-wave in 5; a deep a-wave in 16, and a normal record in 9 eyes, at the end of the stay in oxygen. The changes were as a rule symmetrical. The latent period was not significantly influenced.

In most cases the examination was repeated at least once during the subsequent days or weeks in air. There was a general tendency toward normalizing of the ERG approximately after one week. In Figure 3 the occurrence of a negative ERG is compared in the following groups: (1) animals examined in oxygen, (2) animals examined one to three days after transfer to air, and (3) animals examined one to three weeks after transfer to air. In the first two groups the incidence of a negative ERG is high, whereas in the third group a normal ERG is much more frequent. Typical cases are further illustrated in Figures 4 to 6. Thus it seems that the recorded abnormal negativity in most of the cases is at least partly reversible.

Effect of Long Exposure in Older Kittens.—In order to decide whether the ERG in older kittens reacted in the same way after oxygen exposure, kittens 3 to 4 weeks old were exposed in a similar manner with the same concentrations for 21 to 26 days, and the ERG was recorded before and after the exposure. Five animals were examined. The ERG following the oxygen exposure was normal in eight eyes (Fig. 7). One eye showed a deep a-wave according to the criteria mentioned, and one showed an unusually high b-amplitude, possibly representing a supernormal response. The number of animals examined is too small for definite conclusions to be drawn, but it seems as

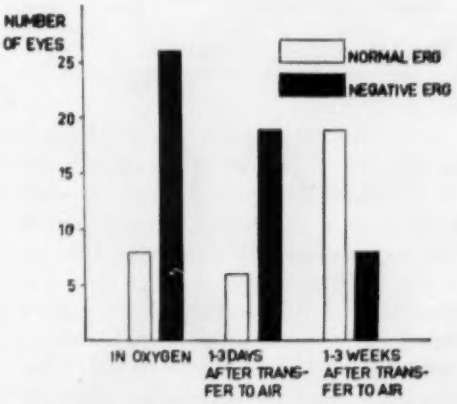


Fig. 3.—Incidence of a negative ERG during the stay in oxygen and afterward in kittens kept in oxygen from birth up to 3 or 4 weeks of age. Light stimulus 800 luxes.

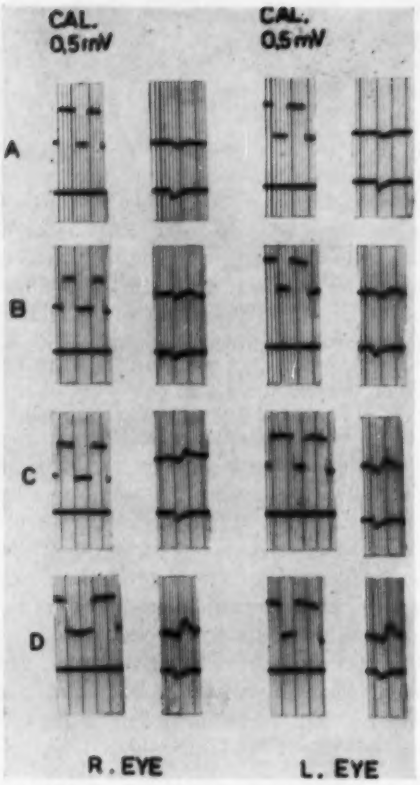


Fig. 4.—ERG of a kitten kept in oxygen from birth up to 21 days of age. Light stimulus 800 luxes, *A*, in oxygen; complete negativity. *B*, three days after transfer to air; dominating a-wave. *C*, eight days after transfer to air; negative a-wave. *D*, 16 days after transfer to air; normal ERG.

though the finding of a negative ERG following oxygen exposure is less frequent in this age group.

Effect of Varying Lengths of Exposure.—In preliminary experiments to establish the shortest time of oxygen exposure that would produce an abnormal ERG, four animals were exposed from the 10th to the 14th day of life to 70% oxygen. Two of them had b-waves of normal amplitude following the exposures; two had only minimal b-waves, symmetrically. In another case the kitten was kept in the incubator at the same concentration of oxygen for 10 days, between the 15th and the 25th day of life. This animal showed in both eyes an ERG with a deep a-wave.

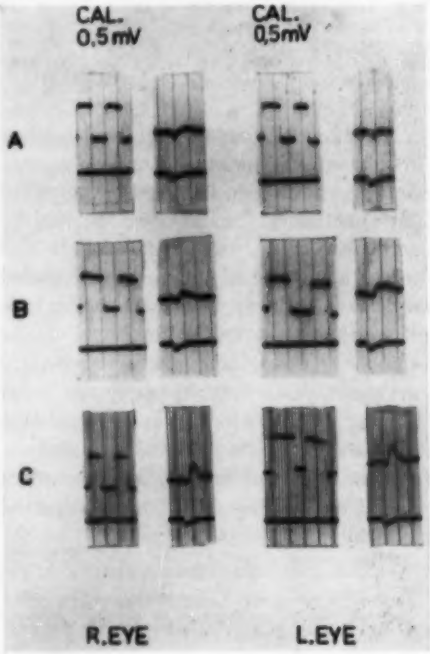
Effect of Ligation of the Common Carotid Artery.—In five kittens, aged from 3 to 6 weeks, the ERG of the right eye was recorded after ligation of the right common carotid artery. This resulted, as has previously been described [14] in a negative ERG (Fig. 8).

COMMENT

The results of these investigations show that the vasoconstriction observed by others after a short time of oxygen exposure in kittens [10] is not accompanied by any constant change in the electrophysiological response to illumination. From this observation, of course, it cannot be concluded that the retinal function and metabolism are unimpaired by the vascular changes. It is well known from experience with human beings that a normal ERG sometimes can be recorded from eyes with pathological changes of the retina, including circulatory disturbances, such as thrombosis of the retinal veins.‡

‡ References 13 and 13a.

Fig. 5.—ERG of a kitten kept in oxygen from birth up to 24 days of age. Light stimulus 800 luxes. *A*, in oxygen; dominating a-wave. *B*, two days after transfer to air; deep a-wave. *C*, seven days after transfer to air; normal ERG.



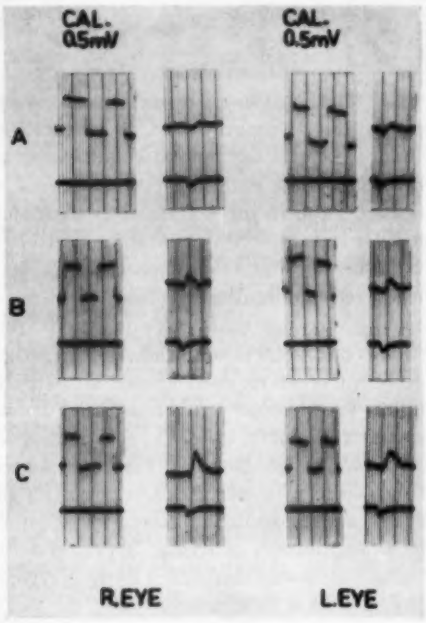


Fig. 6.—ERG of a kitten kept in oxygen from birth up to 21 days of age. Light stimulus 800 luxes. *A*, in oxygen; deep a-wave. *B*, eight days after transfer to air; normal ERG. *C*, 22 days after transfer to air; normal ERG.

In kittens kept in 70% oxygen from birth, the ERG was frequently abnormal at the age of 3 to 4 weeks. The abnormality consisted of varying degrees of negative response, which is a more or less dominating negative a-wave. To interpret this finding, a review of clinical and experimental conditions giving rise to a negative ERG is necessary.

In Karpe's material,‡ in which the ERG during pathological conditions in man was investigated, negative response was seen mostly in cases with acute circulatory disturbances of the retina, such as thrombosis of the central veins or embolism of the central arteries. Henkes [15] found a negative ERG in total occlusion of the central retinal vein and in the majority of the cases of occlusion of the central retinal artery or of a branch artery,[16] whereas supernormal and subnormal responses were frequent in more chronic vascular injuries in hypertensive retinopathy and retinal atherosclerosis.[17]

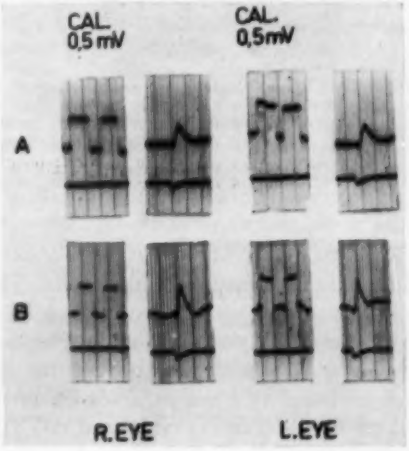
As for experimental studies, Granit,[14] analyzing the components of the ERG, showed that during a progressive ether narcosis P II disappeared first, leaving a purely negative response of P III. Occlusion of the carotid artery in the cat also finally leads to a negative response,[14] a finding which has been confirmed in my own experiments with kittens.

Noell [18] demonstrated a decline of the b-wave during local asphyxia by increasing the intraocular pressure, sufficiently to block intraocular blood circulation, or by general anoxia. There were extensive variations among the species, cat and monkey being most sensitive. In another experiment, with a monkey, a transient blockage of retinal circulation was performed by cutting off the blood supply. Three weeks following this procedure the ERG was recorded, showing a reduced b-wave and a more prominent a-wave than normal. Histological examination revealed a degeneration of ganglion cells, the nerve fiber layer, and the inner nuclear layer, whereas the visual cell layers were entirely normal.

A reduction of the b-wave in rabbits following anoxia or ischemia has also been observed by several investigators.§

§ References 19 to 21.

Fig. 7.—ERG of a kitten kept in oxygen from 4 weeks of age for 26 days. Light stimulus 800 luxes. *A*, before oxygen; normal ERG. *B*, after oxygen; normal ERG. The higher amplitude probably corresponds to the more advanced age.



In most of the investigations mentioned above, the structures responsible for the normal electrophysiological response have been deprived of a normal oxygen supply in one way or another. It has also been possible to injure retinal cells by cytotoxic agents, thus producing abnormal electroretinographic records.

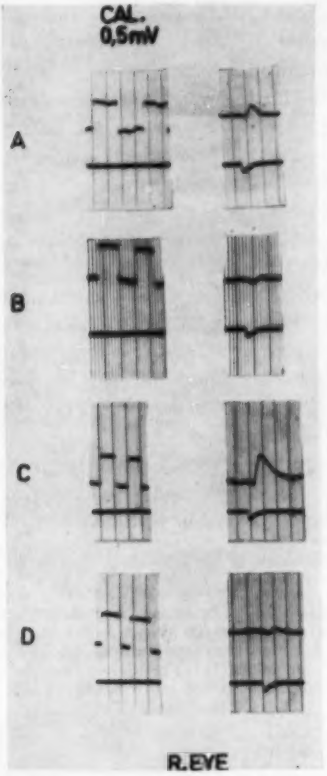


Fig. 8.—ERG of kittens following ligation of the right common carotid artery. Light stimulus 800 luxes. *A*, 20 days old before ligation; normal ERG, *B*, the same six hours after ligation; negative ERG. *C*, 6 weeks old before ligation; normal ERG. *D*, the same six hours after ligation; negative ERG.

Noell [18] has studied the effect of iodoacetic acid on retinal excitation in rabbits. The poison initially abolishes the b-wave only, giving an ERG with dominating a-wave. Praglin and associates [22] explored the influence of methanol and its oxidation products on the ERG in the rabbit and cat. The b-wave was eliminated, and a P III type of ERG was produced.

It is known from Ashton's experiments with kittens [6] that in prolonged hyperoxia the retinal vessels remain closed, as long as the animal is kept in oxygen. It would not seem unreasonable to interpret the finding of a negative ERG in these animals as a sign of retinal ischemia, since this type of ERG is so frequently found in other types of disturbed retinal circulation. This view is supported by the fact that both phenomena, the retinal vaso-obliteration and the negative ERG, in oxygen-exposed kittens are largely limited to the same age group, that is, in kittens from birth up to. approximately 3 weeks of age. The fact that the ERG seems to normalize in most cases after transfer to air is also compatible with the restoration of the normal history of retinal layers, in spite of abnormal revascularization in the oxygen-induced disease in kittens.[6]

It cannot, however, be excluded that a direct cytotoxic effect of the oxygen occurs, as has frequently been suggested, possibly through the interference of enzymes containing sulfhydryl groups.[23] In recent preliminary reports by Noell ‖ this view is supported. Adult rabbits were exposed to oxygen poisoning (60% to 100%) at ambient pressure. Significant attenuation of the ERG became manifest at from 20 to 36 hours of 100% oxygen, at from 50 and 90 hours of 75% to 80% oxygen, and, variably, at 100 hours of 60% to 65% oxygen. Full recovery occurred if exposure was terminated at an early stage, but prolonged exposure rendered recovery incomplete. Histological examination then revealed a selective degeneration of the visual cells. These changes were the same as those after poisoning with intravenous iodoacetate. Degeneration of more than 70% of the visual cell population resulted from exposure for 48 hours to 100% oxygen. These effects strikingly contrasted with the apparent well-being of the animals soon after exposure.

To ascertain if a similarly selective primary cell damage is produced in kittens fol-

‖ References 24 and 25.

lowing oxygen exposure, an extension of the study is necessary, including a histological examination of the eyes.

Irrespective of whether the mechanism of oxygen injury in the retina of kittens is primarily ischemic or cytotoxic, the following conclusion from the present investigation can be drawn: Retinal damage reflected in an abnormal ERG occurs while the animal is still in oxygen. There is no evidence that the transfer of the animal to air implies an exaggeration of this disturbance; on the contrary, the succeeding vasoproliferating phase is electroretinographically accompanied by a restoration to normal.

If identity is accepted between the oxygen-induced disease in kittens and the early stages of retrolental fibroplasia in premature infants on the basis of their close histological resemblances, this would imply that the vasoproliferating stage, commonly described as the first clinical stage of the disease, actually is a secondary phase and that a metabolic injury had already occurred when this phase was starting. If the conception is valid that the vasoproliferating changes represent a reactive, reparative phase, it remains to be explained why in premature infants this reaction sometimes is so excessive as to cause the well-known residual lesions, with vitreous organization and retinal detachment, thus decreasing the function of the eye.

SUMMARY AND CONCLUSIONS

The electroretinogram (ERG) was used as a source of information concerning the influence of oxygen exposure on retinal function in kittens.

Exposure to 85% to 95% oxygen for 10 to 13 hours did not cause any significant changes in the ERG in 2-week-old kittens. Kittens raised from birth up to 21 to 28 days of age in 70% oxygen frequently showed an abnormal, negative ERG. Older kittens did not show the same sensitivity. This observation indicates an injury to the retina, which can be explained either on the basis of ischemia caused by vaso-obliteration or as a direct cytotoxic effect of oxygen.

There was no evidence of an aggravation of the abnormality of the ERG on transfer to air; on the contrary, most abnormal ERG's tended to normalize in a few weeks.

The significance of these findings for the interpretation of the mechanism of oxygen injury in the pathogenesis of retrolental fibroplasia is discussed.

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The gas mixture was supplied by Svenska Aktiebolaget Gasaccumulator (AGA), Stockholm- Lidingö.

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Necroscleritis Nodosa

Clinicopathologic Report of a Case

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Necroscleritis nodosa, a degenerative condition of the sclera of unknown etiology, has only recently been recognized as a clinical entity. Its pathologic characteristics are as yet not sufficiently known to enable the ophthalmologist to differentiate this disease from brawny scleritis or scleromalacia perforans.

HISTORICAL BACKGROUND

Van der Hoeve (1930) presented before the Dutch Ophthalmological Society two cases of a new degenerative entity of the sclera which he named scleromalacia perforans. The same author,[1] in 1934, reported in more detail two of Rochat's cases [2] and two of his own. Verhoeff and King [3] and, more recently, Franceschetti and Bischler [4] clarified this constitutional entity. They emphasized its differential diagnosis and separated it from simulating scleral diseases. Franceschetti suggested that the term perforating scleromalacia should be reserved for cases with little or no inflammatory reaction and associated with rheumatoid arthritis. The term nodular necrotizing scleritis, on the other hand, was suggested to designate cases exhibiting inflammatory process and generally not associated with rheumatoid arthritis. Since then comprehensive articles by François,[5] Anderson and Margolis,[6] and others * have further stressed the clinical and pathologic aspects of this condition.

This paper is the report of a case of necroscleritis nodosa which presented several interesting features and was a difficult diagnostic problem.

REPORT OF A CASE

The patient, a 72-year-old woman, had an intracapsular cataract extraction of the left eye in June, 1953, by one of us (M. A. P.), with an uneventful postoperative course and 20/15 corrected vision. An immature senile cataract was observed in the right eye, which was otherwise normal. She was not seen again until Jan. 27, 1955, when she was admitted to the University Hospital complaining of severe irritation and pain in her right eye, which had been present since October, 1954. In December the patient had exhibited to dermatological examination hemorrhages and papulosquamous, pruritic lesions scattered over the entire body but mainly concentrated on the lower extremities. She was treated by a competent ophthalmologist at that time with Cortomyd solution (a suspension containing cortisone acetate, 1.5%, and sodium sulfacetamide, 10%), neomycorsone (Neosone) ointment, vitamins, and meperidine (Demerol) for her pain. The dermatologist found a nonspecific dermatitis, which he believed was a toxic hemolytic affair, possibly due to the acetylsalicylic acid that the patient had taken for years for headache. A biopsy on one of the skin lesions showed a nonspecific dermatitis. The possibility of ocular pemphigus was entertained by the ophthalmologist. No definite diagnosis, however, could be established, and the patient was transferred to the University Hospital for further studies. On the day of admission to the hospital the right globe was markedly injected, presented spastic entropion of the right lower lid, considerable pain, and photophobia. A dirty, grayish exudate was present in the lower fornix. The corrected visual acuity was counting fingers at 1 meter in the right eye and 20/20 in the left eye.

Slit-lamp examination of the right eye revealed several yellowish corneal infiltrates inside the limbus, with faint fluorescein staining, a large yellowish nodule in the sclera near the limbus between

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Department of Ophthalmology (Dr. Petrohelos) and Laboratory of Neuropathology and Neuro-Ophthalmology (Dr. Wolter), Neuropsychiatric Institute, University Hospital.

* References 7 to 10.

7 and 8 o'clock, and ciliary flush and tenderness. Aqueous flare and cells and posterior synechiae were observed. There was a dense, sclerosed nuclear cataract. Slit-lamp examination of the left eye was otherwise normal except for aphakia.

The ophthalmoscopic examination of the right eye, through hazy media, disclosed no abnormality except that the optic disc was somewhat hyperemic. Ophthamoscopic examination of the left eye was negative. The tonometer tension measured 20 mm. Hg (new Schiøtz) O. U.

The dermatologic examination revealed fading, chemotic, somewhat pruritic lesions over both lower extremities. The patient was referred to the allergy department, but no definite diagnosis could be made. The arthritis unit found no signs of rheumatoid arthritis and/or nodules. A mild osteoarthritis, involving the terminal interphalangeal joints of the fingers and the spine, was present. An increased capillary fragility, as evidenced by the Rumpel-Leede test, was noted. X-rays of the upper and lower intestinal tract and the chest were negative. Sigmoidoscopic and gynecological examinations were negative. Laboratory studies revealed a hemoglobin of 10.9 gm/100 cc., or 70% of normal; a red blood cell count of 4,200,000; a hematocrit reading of 38; a sedimentation rate of 29 mm. in one hour, and a white blood cell count of 9500. Differential count showed 77 polymorphonuclear leucocytes, 15 lymphocytes, 1 monocyte, 2 eosinophiles, and 5 basophiles. The blood Kahn test was negative. Results of the liver battery test were as follows: (*a*) total serum bilirubin 0.4 mg. per 100 cc.; (*b*) free, 1 minute, none; (*c*) free, 30 minutes direct, 0.3 mg. per 100 cc.; (*d*) γ-globulin, 8.1 units per 100 cc.; (*e*) thymol turbidity, 1.2 units; (*f*) cephalin flocculation, 0 in 24 hours and ±2 in 48 hours. Some abnormality of the peripheral blood and bone marrow, characterized by decrease in platelets, was suggested by the laboratory studies, but no specific diagnosis could be made. A blood transfusion was advised.

The spastic entropion responded to alcohol injection. Atropine 1%, phenylephrine (Neo-Synephrine) 10%, chloramphenicol (Chloromycetin) 0.5%, and hydrocortisone acetate 2.5% were applied locally, with scarcely any improvement in the ocular disease. A biopsy of the conjunctiva revealed no pathology other than that of inflammation. Systemic cortisone was added to the above-mentioned regimen, with no effect on the eye condition. Four weeks later the nodule eroded, and the thick, white granulation tissue could be seen underlying the thin conjunctiva (Fig. 1). Several weeks later a similar small nodule developed superiorly and nasally near the limbus, between 1 and 2 o'clock. Despite the local and systemic application of hormones, no improvement was observed, and at the request of the patient the globe was enucleated in April, 1955.

Clinical Comment

As illustrated in this case, the clinical differential diagnosis of inflammatory scleral lesions is sometimes difficult. Perforating scleromalacia occurs in persons past 50 years of age, mostly women, who are usually affected with rheumatoid arthritis. It is bilateral and noninflammatory. As described by Franceschetti,[4] paralimbic scleromalacia, characterized by a single noninflammatory, progressive lesion near the limbus, occurs in persons between 20 and 30 years of age and apparently is not related to arthritis. In senile hyaline scleral plaques, bilateral noninflammatory, gray depressions develop anterior to the insertion of the horizontal recti and seldom, if ever, perforate. The intercalary staphyloma of advanced glaucoma might be confused momentarily as a part of a generalized syndrome. Scleromalacia associated with porphyrinuria is reported in the literature.[10] In necroscleritis nodosa one eye is involved in the majority of cases. It occurs in persons past 50 years of age and exhibits one or more localized rheumatoid nodules (Aschoff) in the sclera. It is not associated with rheumatoid arthritis.

Pathologic Study

Method.—Immediately after enucleation the eye was fixed in bromformalin (Cajal solution). One-half the eye, with part of the affected areas of sclera and cornea, was embedded in paraffin, cut in serial sections, and stained with hematoxylin and eosin. From the other half of the eye sections were made on the freezing microtome and impregnated by the silver carbonate methods of del Rio Hortega.[11] The latter technique has proved to be very useful in demonstrating the histologic details of tissues of the eye under normal and pathologic conditions.†

Pathologic Description.—Macroscopically, the areas of scleral inflammation, as described above, were clearly visible and appeared as distinct loci at the temporal and nasal portions of the limbus, which were white and slightly elevated (Fig. 1). The affected area at the temporal limbus, measuring about 4 mm. in diameter, occupied mainly the perilimbal sclera but also extended into the cornea.

† References 12 to 18.

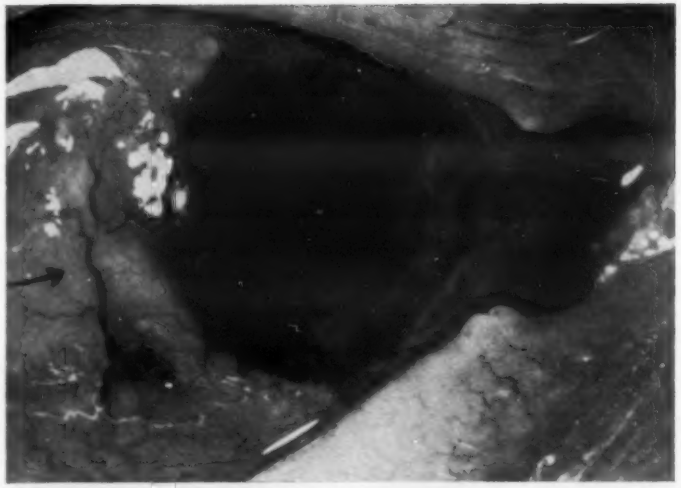


Fig. I.—Clinical aspect of the nodule at the temporal perilimbal sclera of the right eye. The thick, white granulation tissue can be seen underlying the thin conjunctiva.

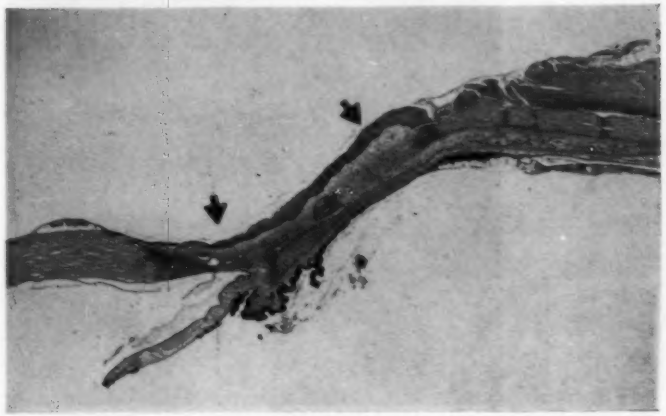


Fig. 2. — Low-power view of a section of the temporal ocular wall with the large granuloma which replaced the sclera (between arrows). The edges of the sclera and the island-like residual of sclera in the middle of the granuloma are necrotic and more eosinophilic than normal scleral tissue. Reduced about 10% from mag. × 10; hematoxylin-eosin stain.

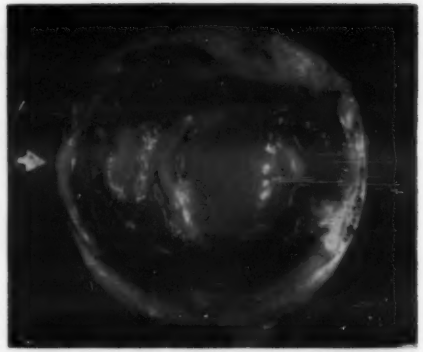
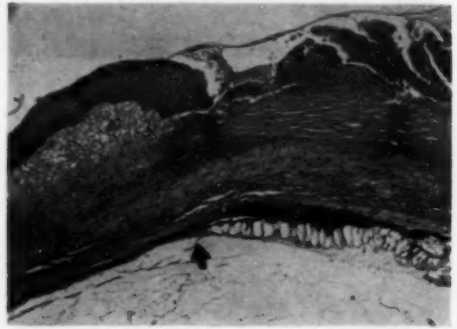


Fig. 1.—Frontal view of the eye after enucleation and fixation. Arrow points to the large nodule at the temporal limbus. The smaller nodule is visible at the nasal limbus. × 12.

Fig. 3.—Higher-power view of the posterior part of the granuloma and the edge of the sclera (arrow) from the same section as that in Figure 2. The granuloma, the necrotic edge of sclera, the infiltration of episclera and choroid, and the cystoid degeneration of the underlying retina are clearly visible. × 30; hematoxylin-eosin stain.



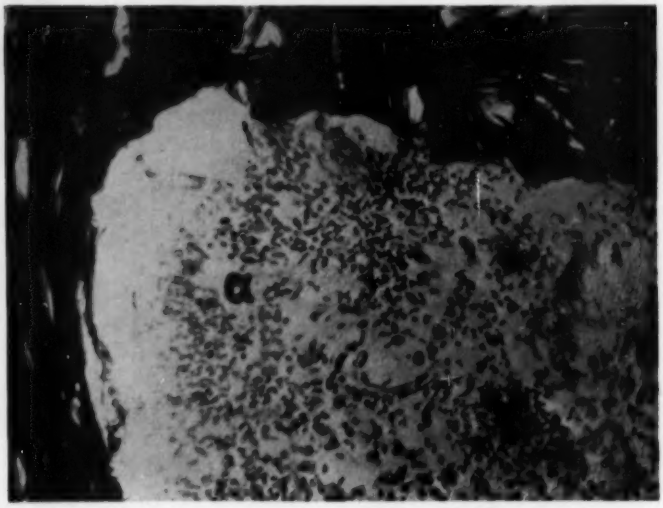


Fig. 4.—An area of the granuloma (a) with sharp limitation to the sclera (scleral tissue stained black). × 300; Hortega method.

After division of the eye, it could be demonstrated that the ocular wall in the area of the larger nodule was about twice as thick as, and much denser in consistency than, that of the other areas. At the limbus, opposite this large nodule, there was another small process of the same nature (Fig. 1). The eye was macroscopically normal with the exception of these two infiltrated areas at the corneal limbus.

Microscopically, the affected area at the temporal limbus appeared as a large nodule extending into the episclera, peripheral choroid, ciliary body, and cornea. Histologically it presented necrobiotic destruction of scleral fibers, inflammation, and the development of an irregular granulation tissue. The necrobiosis of the collagenous fibers of the sclera was the predominant feature of the histologic picture. Figure 2 clearly reveals the extensive defect of sclera and cornea, with the breakdown of the collagenous fibers and their replacement by granulation tissues (area between arrows). In the center of this infiltration an eosinophilic island-like residual of swollen and necrotic sclera had survived and contained no cellular infiltrate (Fig. 2). The borders of the surrounding sclera and cornea consisted of swollen, necrotic collagenous material (Fig. 3). There were many remnants of collagenous fibers throughout the area of granulation.

Fig. 5.—Another area from the edge of the scleral granuloma with diffuse infiltration of scleral tissue. The black structures represent the intertwined scleral fibers. × 400; Hortega method.

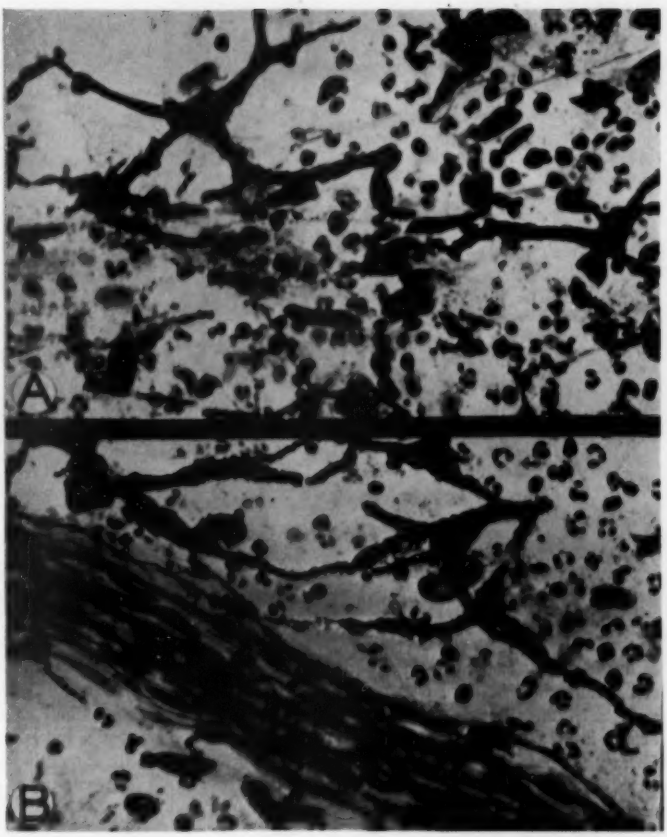


Fig. 6.—*A*, choroid underlying the granuloma with dense infiltration of leucocytes, lymphocytes, and plasma cells. The star-shaped melanoblasts are normal. *B*, another area of the choroid underlying the granuloma, showing inflammatory infiltration of an area which contains a nerve bundle besides the melanoblasts. × 700; Hortega method; horizontal sections.

A dense inflammatory infiltrate surrounded the central island of necrotic collagenous material and filled the space of the destroyed sclera and cornea. The boundary between the infiltrate and the scleral tissue was most frequently sharp (Fig. 4). In some areas, however, there was diffuse infiltration of the scleral fibers (Fig. 5). The infiltrate was composed of epithelioid cells, giant cells, fibroblasts, leucocytes, lymphocytes, and plasma cells. The epithelioid cells were very numerous and mainly

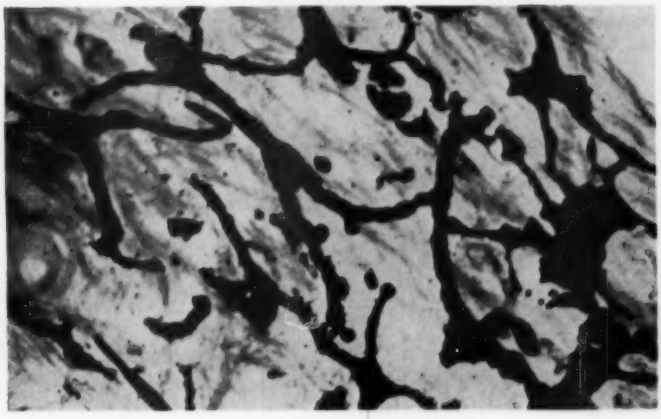


Fig. 7.—Horizontal section of choroid from the central area, which is normal and shows no infiltration. The black structures represent normal star-shaped melanoblasts. × 700; Hortega method.

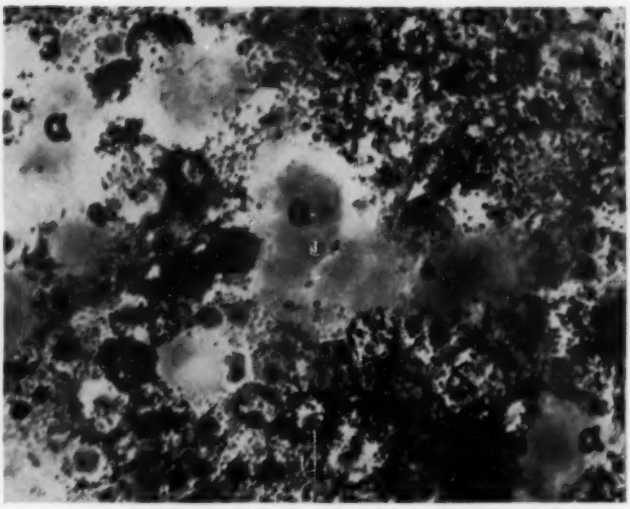


Fig. 8.—Horizontal section through the layer of the pigmented epithelium in the centrum of the retina, showing many confluent drusen (hyaline bodies) of Bruch's membrane (*a*). The drusen have replaced pigmented cells. ×400; Hortega method.

formed an irregular, network-like pattern throughout the granulation tissue. Only rarely were palisade-arranged epithelioid cells noted around the remnants of collagenous material. A few giant cells of the Langhans type, with a relatively small number of nuclei, were observed in areas of dense epithelioid cell formation. Undifferentiated swollen fibroblasts were seen all through the infiltrate. They were denser in areas where the destruction of the scleral fibers was complete. Most frequently the leucocytes were eosinophiles, which were piled up around the necrotic collagenous material. Leucocytes, lymphocytes, and many plasma cells had also infiltrated the episclera, the underlying area of the ciliary body, and the peripheral choroid (Fig. 6). The nodule was covered with an intact conjunctival epithelium. The smaller process, at the nasal limbus, showed the same histologic picture as that just described but was not so characteristically developed.

The dense infiltration and necrobiosis of the sclera was limited to the two nodules described above. There was a slight infiltration, however, with lymphocytes and plasma cells all through the iris, ciliary body, and peripheral choroid. In addition to the infiltration, the peripheral choroid and ciliary body showed some increase in connective tissue and edema, exudation, and congestion.

Complete examination of the eye with the methods mentioned above revealed that there was much damage not only in and around the scleral

Fig. 9.—Section showing the optic nerve head with a large drusen (arrow). ×100; hematoxylin-eosin stain.

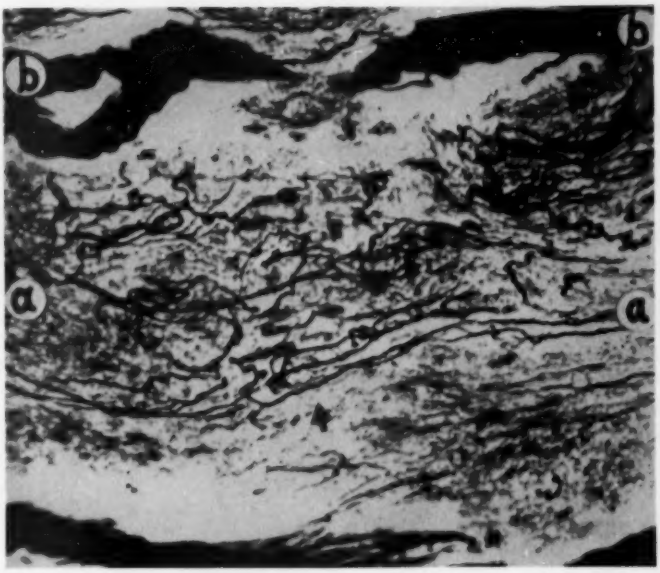


Fig. 10. — High-power view of optic nerve after nerve-fiber-staining technique. Most nerve fibers have disappeared. The remaining fibers are broken, irregularly swollen, and curled (arrow); *a—a*, direction of nerve fibers; *b*, parts of the connective tissue trabecular system. × 700; Hortega method.

nodules but also through the retina and optic nerve. The retina underlying the nodule showed severe cystoid degeneration and proliferation of the pigmented epithelium (Fig. 3). There were severe degenerative changes throughout the retina, with gliosis and breakdown of nerve elements, especially in the ganglion cell layer and the nerve fiber layer. Impressive degenerative damage could be demonstrated in the optic nerve head. There were severe gliosis and associated various-sized drusen (Fig. 9). The nerve fibers of the optic nerve had partially disappeared; others represented interrupted, swollen, and wavy structures (Fig. 10). Swollen microglia cells (gitter cells, or granular compound corpuscles), loaded with fat, were observed surrounding the blood vessels. The choroid of the posterior pole of the eye was normal (Fig. 7), but there were many drusen (hyaline bodies) of Bruch's membrane, which had partially replaced the pigmented epithelium (Fig. 8).

Pathologic Comment

The pathologic examination suggested that the inflammatory scleral process must be classified in the group of true rheumatoid granulations. The clinical diagnosis of necroscleritis nodosa could be confirmed only to a limited degree, since the essential pathologic processes of necroscleritis nodosa, brawny scleritis, and scleromalacia perforans apparently are similar.‡ The histologic feature common to all these diseases is the formation of rheumatoid nodules in the sclera, which are not always typical. In the literature, discrete scleral nodules of this type, without much congestion or infiltration of surrounding tissue, and sometimes producing punched-out defects, are considered to be the typical findings in necroscleritis nodosa,[10] as well as in necroscleritis nodosa excavans.[8] Typical brawny scleritis is reported to demonstrate more diffuse scleral pathology, characterized by marked thickening of the ocular wall and congestion and infiltration of the surrounding tissue of the entire eye.[10]

The scleral process in our case represented in some areas the typical structure of necrobiotic rheumatoid nodules, which were limited sharply. In addition, however, there were observed diffuse scleral infiltration, pronounced thickening of the ocular wall, congestion, edema, exudation and infiltration of the surrounding tissues, and severe degenerative damage throughout the retina

‡ References 3, 6, and 19.

and optic nerve. This histologic picture may be considered to be that of necroscleritis nodosa, but it also could be that of the other two diseases mentioned above. Apparently, necroscleritis nodosa is an entity which as yet can be recognized only clinically, while its pathologic picture is not yet sufficiently well known to be differentiated from brawny scleritis and scleromalacia perforans.

Hyaline bodies, or drusen, of the optic nerve head under different conditions have been described recently by Chamlin and Davidoff.[20] In the present case we were unable to decide whether the presence of the drusen in the optic nerve head was a consequence of the associated degenerative changes in the optic nerve or an independent finding. The presence of drusen (hyaline bodies) in Bruch's membrane of the choroid was assumed to be caused by hyaline degeneration of aging and was not considered a result of the necroscleritis.

SUMMARY

A case of necroscleritis nodosa is reported. The clinical and pathologic features of this condition are analyzed, and the differentiation from related scleral diseases is discussed. There is no known specific treatment for necroscleritis, and in this case hormonal therapy has been of questionable value.

University Hospital.

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Tests for Color Deficiency Based on the Pseudoisochromatic Principle

A Comparative Study of Several New Tests

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Tests composed of pseudoisochromatic plates provide one of the simplest methods of distinguishing between normal and deficient red-green color perception. During World War II the only such test generally available in the United States was the series of 46 plates printed by Beck & Co. and distributed by the American Optical Company. In several investigations reviewed by Farnsworth and Kimble,[1] it was shown that this series included many poor plates, some of which were failed almost as frequently by normal as by color-deficient subjects. To obtain a shorter and a more efficient dichotomous test, various selections of the more highly diagnostic plates were proposed. One of the earliest, a selection of 17 plates, known as the Abridged AOC Test,[2] has been used since about 1944 by the Army Air Forces. A selection of 18 plates was proposed by Hardy, Rand, and Rittler,[3] in 1947, sponsored by the Inter-Society Colour Council and distributed by the American Optical Company, as a replacement for the original 46-plate test. It will be referred to hereafter as the Revised AO test. The test distributed by Armin Jacobs is a reprint of the same 18 plates, which has not been evaluated experimentally.

Of the new tests which have recently become available in this country, several show promise of being superior to the various abridged versions of the American Optical Company test.

DESCRIPTION OF TESTS INVESTIGATED IN THIS STUDY

The three new tests investigated in this study are (*a*) the Dvorine Plates, issued in 1953 and reprinted in 1955; (*b*) a new edition of the Ishihara plates, published by Handaya & Co., in Japan (date not given), and (*c*) the AO-HRR plates, issued in 1955. For comparison with these three, we included an experimental test composed of 20 of the more highly diagnostic plates selected from four different American and European tests. This will be referred to hereafter simply as the 20-plate test.

Dvorine Test.—This comprises 14 testing plates containing numerals to be read and 7 containing paths to be traced. The latter are for the testing of young children and other illiterates. They were not used in this study, since the pairs of confusion colors are the same as those of the 14 number plates. Of the seven pairs of confusion colors, five attempt to reproduce color combinations shown in a previous study[4] by one of us (L. S.) to be highly diagnostic. Data on this test have been published by Dvorine, by

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Peters, and by Crawford. Dvorine [6] examined an unselected group of 118 male subjects. Of the 103 classed as having normal color vision, 98 made no errors, and 5 made one error, in reading the 14 plates. Of the 15 subjects classed as color-deficient, 10 failed all 14 plates, and 5 had error scores ranging from 5 to 13. No other test of color deficiency was given.

Peters [6] compared the Dvorine with the Revised AO test. With a passing score of 3 or less errors on the 14 plates of the former, and 4 or less on the 18 plates of the latter test, the classification was the same for 97 of the 101 subjects. Four who passed the Revised AO test failed the Dvorine test, with error scores of 4, 4, 5, and 7, respectively. In a second study by Peters,[7] a group of 800 male subjects were given the Dvorine test, and a different group, of 638, the AO test. The percentage failing the Dvorine test (4 or more errors) was 7.75, which agrees closely with previously published figures on the frequency of red-green color deficiency among males. In the group given the AO test, only 3.29% failed. This result is difficult to explain unless it is assumed that, because the subjects were candidates for appointment to the police force, some of those with deficient color perception had memorized the AO plates to avoid disqualification.

Crawford,[8] using an anomaloscope as the criterion, compared the Ishihara (Ninth Edition) and the Dvorine test as to their ability to distinguish between normal and deficient color perception. The 65 normal subjects made 2 or less errors on the 14 Dvorine plates. Of the 11 color-defective subjects, 1 made 3 errors; the others, 9 or more. On the 20 plates of the Ishihara test, the normal subjects made 5 or less errors; one color-defective subject made 6 errors; the others, 12 or more. Both tests, therefore, show complete agreement with the anomaloscope in the classification of the subjects as either normal or color-deficient if 2 or less errors are permitted on the Dvorine test and 5 or less on the Ishihara test.

Ishihara Test.—In the latest edition of the Ishihara test there are 16 test plates with digits and 7 with paths. The latter were not used in this study. The two plates whose digits are more easily seen by the color-deficient than by the normal observer were also omitted. No evaluation of this test has been published. Its confusion colors are, however, similar to those employed in previous versions, such as those evaluated by Hardy, Rand, and Rittler.[9] In their study the 74 subjects classed as color-deficient by other criteria all failed 5 or more of the 12 plates; and none of the 32 subjects classed as normal failed more than 4 plates.

AO-HRR Test.—This series of plates, developed by Hardy, Rand, and Rittler and distributed by the American Optical Company, differs in several important respects from other pseudoisochromatic tests. It includes plates for blue-yellow, as well as for red-green, deficiencies. Instead of digits, it uses three simple geometric forms. The background of all plates is a neutral gray. The dominant wave lengths of the colors used for the figures approximate the spectral and nonspectral neutral points of the several classes of dichromats. A red or a bluish-green figure, for example, is used to detect protans; a bluish-red or a green figure, to detect deutans. Colors of low saturation are used in the "screening" plates to distinguish between normal and deficient color perception. The same colors in three higher saturations are used to identify the type and measure the degree of defect.

The three published studies pertaining to this test all report data obtained with the preliminary experimental set of plates, which differ in some respects from those of the second version, distributed by the American Optical Company. Our own study of the first version [10] was concerned primarily with its ability to diagnose the type and degree of red-green color deficiency and did not report any data on its efficiency as a dichotomous or screening test. Schmidt [11] compared these plates with the Nagel anomaloscope and with three other pseudoisochromatic tests, namely, the Ishihara, the Boström-Kugelberg, and the Abridged AOC. Using as a criterion the combined results of the several tests, she

found that the three screening plates of the HRR test classified correctly all subjects with deficient red-green color perception but misclassified a significant proportion of the normal group (3.4% in one series, 4% in another).

In the studies published by Hardy, Rand, and Rittler,[12] the Revised AO test was used as a criterion, with a passing score of 4 or less errors on its 18 plates. All 630 subjects who passed the criterion test read the three screening plates without a single error, and all 150 who failed made one or more errors on the screening plates.

In the second version of the test there are four "screening" plates for red-green deficiencies. Errors in reading these plates are not counted if all responses are correct on a second trial. In unpublished studies by Hardy, Rand, and Rittler,* in which the first and second versions of the test were given to 263 subjects, there were only 2 instances of disagreement in the classification of subjects as normal or as color-deficient on the basis of the screening plates.

Twenty-Plate Test.—This group of plates, assembled from four different tests, has been in use in our laboratory since 1950 and has proved of value in borderline cases because of the relatively high error scores made by subjects with only slight defects. It is composed of six plates from the Abridged AOC test, five each from the Boström-Kugelberg and the Polack test, and four from the 1940 and 1947 Dvorine tests (Table 7). An initial group of 60 plates was studied, and from these the 20 with the highest diagnostic efficiency were selected by procedures described elsewhere.†

EXPERIMENTAL PROCEDURE

Subjects were obtained from two sources. The first group comprised males aged 8 years or over, without ocular disease or abnormality other than refractive error, but otherwise unselected. This group provided all those eventually classed as normal. The second group, the color-deficient subjects, were obtained from various sources. The majority were referred to our laboratory for evaluation of their color vision after failure or questionable failure on some single test given elsewhere. Any who showed evidence of ocular disease or abnormality were excluded from this study. Since many were examined before this investigation was planned, and before all four of the pseudoisochromatic tests were available, complete data were not obtained from all the color-deficient subjects. Deficient color perception was, however, confirmed in each case by other tests. These included the Nagel Anomaloscope, the Color Threshold Tester, the Farnsworth-Munsell Dichotomous Test, and the F-M 100-Hue Test.

The source of illumination for the pseudoisochromatic tests and for the 100-Hue and Dichotomous Tests was a Macbeth Daylight Lamp (approximately 6500° K, illuminance about 25 f-c.). The order in which the pseudoisochromatic tests were given was randomized so as to equalize practice effects which might result from similarities among the different plates. The subject was given five seconds to read each plate. An error spontaneously corrected within this time limit was scored as a correct response. On charts of the dual response type, where the normal subject usually sees one number, the color-deficient another, those who saw both were asked to select the more visible. In the rare instances in which both digits were reported as equally visible the response was considered incorrect.

The instructions for the AO-HRR Test state that, if errors are made in reading the screening plates but not in the diagnostic plates, the former may be shown a second time. If there are no errors on retest, the subject is classed as having normal color vision. In this study the order of presentation of the screening plates was changed after 38 apparently normal subjects had been tested. Eight of these 38 subjects gave incorrect responses to Plate 1, which were not repeated on a retest. In the revised order, Plates 5 and 6 (for detecting yellow-blue deficiencies) were shown immediately after the four demonstration plates, followed by Plates 2, 3, 4, and 1 (for detecting red-green deficiencies). When the apparently more difficult Plate 1 was shown last, only 4 of 62 normal subjects made errors on the first showing of the plates. The revised order of the screening plates, therefore, results in fewer instances of such equivocal responses that require administration of the diagnostic plates and repetition of the screening plates.

A difficulty in evaluating any new test for the detection of red-green color deficiency is that there is no generally accepted and completely valid standard with which the findings can be compared. Even the Nagel Anomaloscope classifies as normal an occasional subject who shows obvious color deficiency on other types of test.[14] Good pseudoiso-

* Personal communication to the authors.

† References 4 and 13.

chromatic tests divide most subjects into two distinct groups, with very high and very low error scores. There are, however, usually some who make more errors than the obviously normal subjects, but fewer errors than the obviously color-deficient subjects. Extensive studies of the subjects of this small group are needed in order to determine whether their errors result from a true deficiency in color discrimination or are the result of unfamiliar digit forms or other factors not related to color discrimination. This group with borderline error scores is largely responsible for the lack of perfect agreement among different pseudoisochromatic tests. The correct classification of these subjects as either normal or color-deficient is therefore of particular importance in any comparison of the relative merits of the various tests. In this study all subjects with borderline error scores on any of the four pseudoisochromatic tests were given as many other tests as time permitted.

RESULTS

A. Determination of Passing Scores for Each Test

One hundred subjects were classified as having normal color vision on the basis of the combined results of the four pseudoisochromatic tests. Table 1 shows the distribution of the error scores. In this tabulation all errors made on test and on retest with the four AO-HRR plates were counted. (In the case of subjects making no errors on the first test, a retest was not given and it was assumed that no errors would have been made.) When the two presentations of the AO-HRR plates are counted as equivalent to 8 different plates, the total number of plates in all four tests is 56. Only one of the 100 subjects failed as many as 8 plates, with 3 errors on the 20-plate test, 2 on the Dvorine, 2 on the Ishihara, and 1 on the AO-HRR test. Among the subjects classified as color-deficient both by pseudoisochromatic and by other tests, there was only one whose total error score on the 56 plates was less than 15 (Case 1, Table 4). This subject, though definitely color-deficient, failed only 11 of the 56 plates.

Table 1.—*Distribution of Error Scores of One Hundred Normal Subjects for Fifty-Six Pseudoisochromatic Plates*

Plates Failed				
No.	Per Cent	Frequency	Cumulative	Frequency
0	0	32	0	32
1	1.8	27	1 or less	59
2	3.6	13	2 or less	72
3	5.4	11	3 or less	83
4	7.1	8	4 or less	91
5	8.9	4	5 or less	95
6	10.7	2	6 or less	97
7	12.5	2	7 or less	99
8	14.3	1	8 or less	100

Table 2.—*Distribution of Error Scores of One Hundred Normal Subjects on Each Test*

No. of Errors	20-Plate	Ishihara (14 Plates)	Dvorine (14 Plates)	AO-HRR	
				Test	Retest
0	57	61	76	88	98*
1	27	25	15	10	2
2	10	10	8	2	..
3	6	4	1	..	..
Total	100	100	100	100	100

* It is assumed that the 88 subjects who made no errors on the first test would not have made any errors on a retest if one had been given.

Table 2 shows for the normal subjects the error scores on each of the four tests. These data suggest that 3 or less errors should be considered as indicative of normal color vision on the Ishihara, on the Dvorine, and on the 20-plate test. These passing scores are in general agreement with the usual finding that on different pseudoisochromatic tests comprised of 12 to 20 plates the maximum number of errors made by any normal subject is 25% or less of the total number of plates. On the AO-HRR screening plates, the standard instructions permit no errors on retest. By this criterion, 2 of the 100 normal subjects are misclassified. One of these made no errors on the 20-plate test, 1 error on the Ishihara test, and 1 on the Dvorine test. His single error on the AO-HRR plates was repeated on the retest. The second subject made no errors on the 20-plate and Ishihara tests and 1 error on the Dvorine test. On the four AO-HRR screening plates, he made 2 errors on the first trial, 1 on the second, and none on the third trial. Whether or not it would be advisable to modify the standard passing score on this test so as to permit a single error on retest cannot be determined until the error scores of color-deficient subjects are

TABLE 3.—*Distribution of Error Scores of Color-Deficient Subjects on Each Test*

No. of Errors	Frequency			
	20-Plate	Ishihara	Dvorine	AO-HRR*
0	0	0	0	41† 9.1%
1	0	0	4†	2
2	0 0%	1† 3.1%	1† 5.3%	9 25%
3	0	2†	0	15
4	0	1	0	14 65.9%
5	0	0	1	
6	0	1 4.1%	3 6.4%	
7	1	2	2	
8	3 4%	4	1	
9	3	6	4	
10	0	2 92%	5 88.3%	
11	1	2	6	
12	3	9	12	
13	1	12	10	
14	1	55	45	
15	2 96%			
16	5			
17	9			
18	11			
19	42			
20	94			
Total	176	97	94	44

* These are retest scores in four cases. According to the instructions, the six subjects who made errors on the "screening" plates but none on the "diagnostic" plates should have been given a retest on the former group. This was omitted in two of the six cases.

† Additional data on these subjects who made normal scores are given in Table 4.

studied. Similarly, the passing score of 3 or less errors tentatively adopted for the other three tests, in order to qualify all normal subjects, must be applied to the scores of known color-deficient subjects to see whether it classifies correctly color-deficient as well as normal subjects.

Table 3 shows for each of the four tests the distribution of the error scores of subjects classed as color-deficient. Of the 176 given the 20-plate test, 169, or 96%, failed on more than half the plates and can therefore be considered as definitely color-deficient without reference to other tests. The seven with error scores ranging from 5 to 9 all made typical deuteranomalous matches on the Nagel anomaloscope, with quotients ranging from 2.9 to 4.0.‡ It is highly probable, therefore, that the passing score of 3 or less errors on the 20-plate test classified correctly the entire group, composed of 100 normal and 176 color-deficient subjects.

On each of the other three tests a few subjects made normal scores, although classified as color-deficient by the 20-plate and other tests. Detailed data for each of these cases are given in Table 4. From this Table it may be seen that all made typical deuteranomalous matches on the Nagel Anomaloscope. The fact that they required more green

‡ References 15 and 16.

TABLE 4.—*Additional Data on Color-Deficient Subjects Making Normal Scores on One or More Tests**

Case No.	Error Scores					Anomalous Quotient	CTT Score	Error Score, F-M 100-Hue Test	Other Data
	20-Plate	Ishihara	Dvorine	AO-HRR Test	AO-HRR Retest				
1	7	3	1	0	x	3.5	61	24	Fails 2 of 12 Rabkin plates; maternal grandfather color-deficient
2	8	2	1	x	x	3.1	63	1 panel only given	.....
3	8	6	1	0	x	3.4	54	54	Fails 5 of 12 Rabkin plates
4	8	4	1	0	x	3.4	51	51, 38	Brother has error score of 9 on 20-plate test; anomalous quotient of 2.9
5	9	9	5	1	0	4.0	50	84	No errors on diagnostic plates of AO-HRR; fails 6 of 12 Rabkin plates
6	9	3	2	1	1	3.7	x	x	No errors on diagnostic plates of AO-HRR

* Boldface figure scores are normal. An x indicates that no test was given.

and less red than normal subjects in matching a red-green mixture to yellow is evidence of anomalous color perception but does not by itself prove that color discrimination is poorer than that of the normal subject. Von Hess,[17] for example, believes that such anomalous matches can be attributed to an increased sensitivity to red. Other tests given to this group of subjects indicate, however, that discrimination of red and green is not only anomalous but also inferior to that of normal subjects. The 100-Hue test, given to five of the six subjects, showed definitely poorer hue discriminaiton than that shown by most normal subjects. The numerical error scores listed in Column 8 of Table 4 give the sum of the deviations from a perfect score of 2 for each of the 85 items. The results of this test are shown in the form of error profiles in Figure 1. Scores on the color threshold test are given in Column 7 of Table 4. On this test about 95% of normal subjects and about 12% of color-deficient subjects make scores of 60-64.[18] Scores below 55 are almost never made by subjects with normal color vision and normal visual acuity. The scores of 50-54 made by three of the five subjects given this test therefore suggest a definite, though mild, impairment of hue discrimination for point sources.

It must be concluded that the Ishihara, Dvorine, and AO-HRR tests each failed to detect the deficient color perception of a small group of subjects. It is, moreover, apparent from Tables 2 and 3 that the passing scores tentatively adopted for each test cannot be changed without increasing the number misclassified.

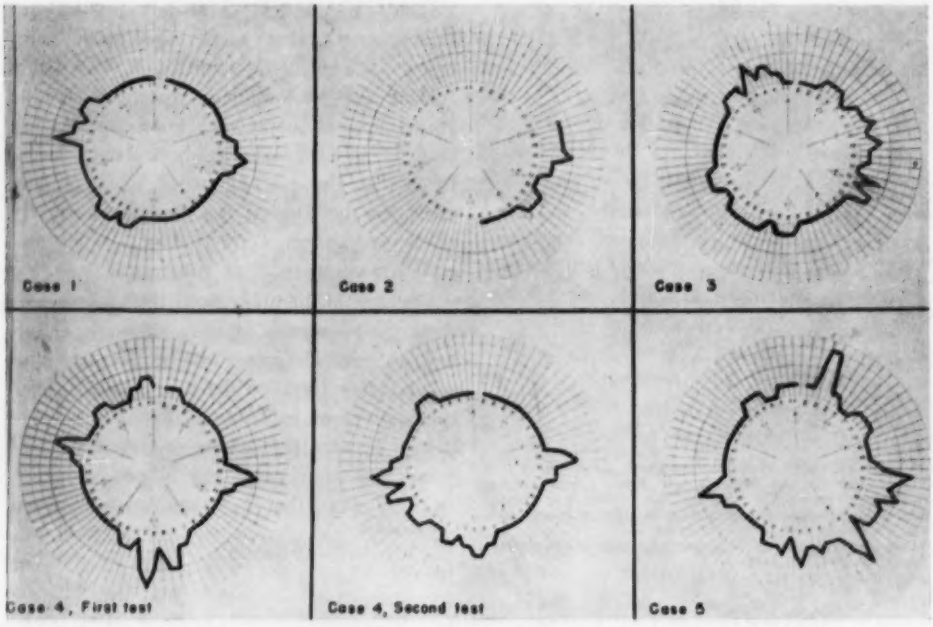

Fig. 1.—Error profiles on Farnsworth-Munsell 100-Hue Test for five subjects who pass one or more pseudoisochromatic tests.

B. Classification of Subjects by Each Test

Table 5 shows the proportion of normal and of color-deficient subjects wrongly classified by each test when these criteria are applied. The 20-plate, Ishihara, and Dvorine tests each classified correctly all 100 normal subjects, whereas 2 of the 100 were mis-

TABLE 5.—*Classification of Subjects by Combined and by Individual Tests*

	Individual Tests*							
	20-Plate		Ishihara		Dvorine		AO-HRR	
Combined Tests	Pass	Fail	Pass	Fail	Pass	Fail	Pass	Fail
Normal color vision.....	100	0	100	0	100	0	98	2
Deficient color vision.....	0	176	3	94	5	89	4	40

* Passing scores on the 20-plate, Ishihara, and Dvorine tests, 3 or less errors; passing score on the AO-HRR test, correct responses to all four screening plates, or, if any are incorrect, correct responses on second trial and correct responses to all diagnostic plates.

classified by the AO-HRR test. Only the 20-plate test classified correctly all color-deficient subjects. Those who passed one or more of the other three tests are the six subjects listed in Table 4. Of the five who took all the tests, two were misclassified by the Ishihara, four by the Dvorine, and four by the AO-HRR test. Of the three commercially available tests, the Ishihara is therefore slightly superior to the Dvorine and AO-HRR tests in the detection of borderline cases of color deficiency. The AO-HRR test is slightly inferior to the Ishihara and Dvorine tests because of its occasional misclassification of normal subjects.

It is of interest to consider the possible reasons for the fact that the 20-plate test proved to be more successful than the other three tests in distinguishing between normal and deficient color perception. It might, for example, be due solely to the greater number of plates. To investigate this possibility, individual error scores were computed for the combined 28 plates of the Ishihara and Dvorine tests. The scores of the 100 normal and the 70 color-deficient subjects given both tests are shown in Table 6. It is apparent that a passing score of 5 or less incorrect responses to the 28 plates must be adopted if all normal subjects are to be correctly classified. This cut-off score, however, fails to detect 4 of the 70 color-deficient subjects, namely, Cases 1, 2, 4, and 6 of Table 4, all of whom failed to pass the 20-plate test. The findings suggest that the individual items of the 20-plate test must be more difficult, at least for those with mild deficiencies, than are the individual plates of the Ishihara and Dvorine tests.

TABLE 6.—*Error Scores for Twenty-Eight Plates of Combined Ishihara and Dvorine Tests*

	Frequency	
No. of Errors	Normal	Color-Deficient
0	82	0
1	24	0
2	11	0
3	9	1
4	3	1
5	1	2
6	0	0
7	0	1
8-12	0	0
13-28	0	65
Total	100	70

TABLE 7.—*Rates of Misclassification of Normal and Color-Deficient Subjects by Individual Plates of 20-Plate Test*

		Q_D Borderline Cases		
Plate No.*	Q_N	Omitted	Included	Source of Plate†
17	0%	0.0%	2.3%	Plate 36, Dv
7	0	1.8	2.8	Plate M, B-K
19	1	1.8	2.8	Plate 22, Dv
10	1	4.7	6.3	Plate C, B-K
11	0	5.9	8.5	Plate N, B-K
8	0	6.5	7.4	Plate K, B-K
15	2	2.4	4.6	Plate 25, P
9	2	4.1	6.25	Plate R, B-K
14	3	1.2	1.1	Plate 34, P
4	3	3.5	5.1	Plate 42, AO
3	3	4.7	8.0	Plate 20, AO
12	0	10.6	13.1	Plate 29, P
1	0	11.2	13.1	Plate 6, AO
5	0	12.9	15.9	Plate 19, AO
16	5	8.8	11.9	Plate 28, P
6	6	2.4	3.4	Plate 29, AO
20	6	5.3	7.4	Plate 2, Dv
13	7	0	0.6	Plate 42, P
2	11	16.5	19.3	Plate 10, AO
18	15	0	1.7	Plate 2, Dvorine 1947 screening test, Group B
Average	3.25%	5.5%	7.07%	

* The plates are listed in order of their over-all diagnostic efficiency, as explained in the text.
† Dv stands for Dvorine, 1940 edition; B-K for Boström-Kugelberg; AO for American Optical Company, 1940 edition; P for Polack.

TABLE 8.—*Rates of Misclassification of Normal and Color-Deficient Subjects by Individual Plates of Dvorine Test*

Plate No.*	Q_N	Q_D Borderline Cases Omitted	Q_D Borderline Cases Included
9	2%	2.3%	7.2%
15	0	4.6	10.7
12	2	1.1	7.2
13	1	10.2	15.5
5	1	11.4	14.5
6	0	13.7	18.6
8	0	14.8	19.6
10	5	4.6	7.2
7	1	18.2	21.6
14	1	20.4	24.8
4	7	4.6	8.3
2	5	20.5	24.8
11	0	26.1	29.8
3	10	2.3	6.2
Average	2.4%	11.1%	15.4%

* The plates are listed in order of their over-all diagnostic efficiency, as explained in the text.

C. DIAGNOSTIC EFFICIENCIES OF INDIVIDUAL PLATES OF 20-PLATE, DVORINE AND ISHIHARA TESTS

A further analysis was made to determine whether the 20-plate test has higher diagnostic efficiencies for all subjects, or whether, perhaps by chance, it is more difficult only for the specific group of subjects listed in Table 4. The percentage of color-deficient subjects passing each plate, Q_D, and the percentage of normal subjects failing each plate, Q_N, are shown in Tables 8 to 10. The values of Q_D were computed both with and without the data for the special group of borderline cases that are listed in Table 4. When these cases are omitted, the values of Q_D for the 20-plate test range from 0.6% to 16.5%, with an average of 5.5%. For the Dvorine test the range is 1.1% to 26.1%, the average 11.1%. For the Ishihara test the range is 0 to 27.5%, the average 8.4%. As regards the difficulty of the individual plates for color-deficient subjects, therefore, the 20-plate test is the most difficult, the Ishihara second, the Dvorine third. Since the borderline cases were not included in computing these values of Q_D, we may conclude that the 20-plate test is more difficult than the other two tests for color-deficient subjects in general, and not merely for the small group of borderline cases.

TABLE 9.—*Rates of Misclassification of Normal and Color-Deficient Subjects by Individual Plates of Ishihara Test*

Plate No.*	Q_N	Q_D Borderline Cases Omitted	Q_D Borderline Cases Included
6	0%	1.1%	5.1%
4	1	0	3.1
13	1	1.1	3.1
3	1	3.3	7.1
12	0	5.5	11.2
2	0	7.7	12.2
16	3	12.1	17.4
9	2	16.5	20.4
10	4	15.4	20.4
5	7	0.0	2.0
17	0	24.2	28.6
8	1	27.5	31.6
7	11	1.1	1.0
11	20	2.2	4.1
Average	4.1%	8.4%	11.8%

* The plates are listed in order of their over-all diagnostic efficiency, as explained in the text.

TABLE 10.—*Rates of Misclassification of Normal and Color-Deficient Subjects by Individual Plates of AO-HRR Test*

Plate No.	No. of Errors 100 N	No. of Correct Responses 38 c.d.	44 c.d.	Q_N	Q_D Borderline Cases Included	Q_D Borderline Cases Excluded
Screening						
1	2*	1	6	2%	2.6%	13.6%
2	0	1	5	0	2.6	11.4
3 and 4	0	9	14	0	23.1	31.8
Mild						
7	0	5	10	0	12.8	22.8
8 and 9	0	7	12	0	17.9	27.2
10	0	18	22	0	46	52.3
11	0	12	17	0	30.8	38.6

* These errors were repeated on recheck.

The values of Q_N listed in Tables 8 to 10 show, for the Dvorine test, a range of 0 to 10% and an average of 2.4%. For the 20-plate test the range is 0 to 15%, the average 3.3%. For the Ishihara test the range is 0 to 26%, the average 4.1%. Misclassification of normal subjects as color-deficient is, therefore, less likely to occur with the Dvorine test than with the 20-plate or the Ishihara test.§

§ Although the 20-plate test has a slightly higher average value of Q_N than the Dvorine test, this is offset by its greater number of plates.

In previous papers || we have discussed methods for obtaining a single index of diagnostic efficiency for each plate of a screening test from its values of Q_N and Q_D. The simplest procedure is a graphical one, in which Q_N is plotted on one ordinate, Q_D on the other, as in Figure 2. For reasons discussed in the previous papers, we consider misclassification of normals to be a more serious defect than misclassification of color-deficient subjects. In Figure 2, therefore, the values of Q_N are plotted on a scale whose units are three times those of the scale for

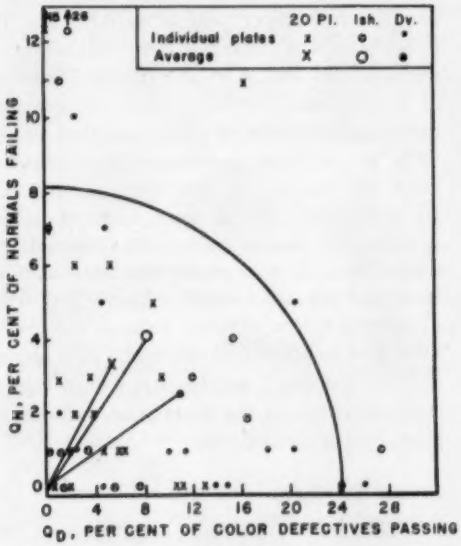

Fig. 2.—Graphic representation of diagnostic efficiencies of individual plates. See text.

Q_D. In a screening test, Q_N and Q_D for the ideal plate would both be zero, and the plotted point would fall at the origin of the graph. The nearer the point is to the origin, the better is its diagnostic efficiency. If the average diagnostic efficiency of a series of plates is high, the minimum number of errors made by a color-deficient subject will be significantly greater than the maximum number of errors made by normal subjects. A marked separation in the error scores of the two groups when the test is properly administered insures that misclassifications will be rare even when extraneous factors are present that reduce the diagnostic efficiency of the test. Such factors include the use of nonstandard illumination, previous coaching of the subject to enable him to memorize the correct answers, failure of the examiner to show all the plates, etc.

The large symbols in Figure 2 represent the average diagnostic efficiencies of the individual plates of the three tests when misclassification of normals is given a weighting of 3 relative to misclassification of color-defective subjects. With this weighting the average efficiencies of the Ishihara and the Dvorine plates are about the same, and both are somewhat poorer than the average efficiency of the 20 plates. The smaller symbols in Figure 2 indicate in a similar manner the efficiencies of the individual plates of each test. In each series there are one or two relatively poor plates. In the Ishihara test, for example, Plate 11 (Q_N, 26%; Q_D, 2.2%) and Plate 7 (Q_N, 11%; Q_D, 1.0%) are definitely inferior to the other 12 plates of this test. Such data are of value in showing where improvements could be made in future editions.

D. Diagnostic Efficiencies of Individual Plates of AO-HRR Test

With certain modifications, a similar analysis can be applied to the individual plates of the AO-HRR test. In the case of plates used to estimate degree of defect, good plates should have low values of Q_N; the Q_D values, however, may be expected to vary with the degree of defect they are intended to detect. In the case of plates failed only by dichromats, for example, the incidence of correct responses from color-defective subjects would be close to 75%. The screening plates and those for the detection of mild defects, on the other hand, should have low values of both Q_N and Q_D. Table 10 gives the rates of misclassification for the four screening plates and for the five plates of the "mild" group. Since all deutans are expected to perceive the single figure of Plate 8, and all protans, the single figure of Plate 9, these two plates were treated as a

|| References 4 and 13.

single unit, and only correct reading of both plates by a color-deficient subject was considered a misclassification. Since Plates 3 and 4 each contain only a single figure, which appears to be relatively easy for one of the two types of red-green deficiency, they were likewise treated as a single plate. This procedure results in a lower rate of misclassification of color-defective subjects than would be obtained if each plate were considered a separate item.

The highest value of Q_N, namely 2%, for Plate 1, compares favorably with the Q_N values of the 48 plates of the other three tests, 18 of which were failed by more than 2% of normal subjects. It is evident, therefore, that the small number of screening plates and the requirement of a 0 error score, rather than poor diagnostic efficiency of the individual plates, is responsible for the occasional misclassification of normal subjects by the AO-HRR test. The Q_D values, on the other hand, are, with two exceptions, higher than those of a majority of the plates of the other three tests. For this reason, increasing the number of screening plates by including those for detecting mild defects and lowering the passing score to permit a single error would probably not make this test as efficient as the Ishihara and Dvorine tests. In our series, for example, this change, though it would reduce the number of normals failing the test from two to zero, would increase the number of color-defective subjects passing the test from four to six.

The high values of Q_D for these AO-HRR plates are somewhat surprising in view of the fact that, for the normal eye at least, the difference in chromaticity between figure and background is less than that of the plates in the other three tests. Two possible explanations suggest themselves. The first is that the particular color combinations of the AO-HRR plates are less difficult for the color-deficient subject than are the majority of the combinations used in the other tests. A second, and more likely, possibility is that the use of simple geometric forms (circles, crosses, and triangles), rather than numerals, makes the task an easier one. Assuming that, to the color-deficient observer, there is a barely perceptible difference between the colors of figure and background, it might be easier for him to distinguish between two ¶ or three possible geometric forms than to identify correctly both components of a two-digit numeral. This possibility could be tested experimentally if a new test were constructed, using the same color combinations but substituting numerals for the geometric forms.

The 2% rate of misclassification of normal subjects by the AO-HRR test, if confirmed in a larger series, would make it inferior as a screening test to the Ishihara and Dvorine tests.# A 2% misclassification of normal male subjects cannot be considered negligible in view of the fact that about 92% of the male population have normal color perception. If, therefore, no test at all were given and all were assumed to be normal, the number misclassified would be about 8%. A test which misclassifies, for example, 2% of normal subjects and 6% of color-deficient subjects reduces the overall rate of misclassification from 8% to about 2.3%. One which misclassifies 6% of color-defective subjects but no normals reduces it from 8% to about 0.5%.

SUMMARY AND CONCLUSIONS

1. The excellent results obtained with the special selection of 20 plates of high diagnostic efficiency indicate that, in future evaluation of new screening tests for red-green color deficiency, this group of plates could serve as the single criterion for classifying subjects as either normal or deficient.

2. The Ishihara, Dvorine, and AO-HRR tests all detect the great majority of those

¶ Since the two forms on a given plate are never the same, when the subject sees one of them, he has a choice of only two answers for the second.

This applies only to the use of the AO-HRR plates as a screening test for red-green color deficiency. The fact that this test also gives information as to the type and the degree of defect makes it more generally useful than any other pseudoisochromatic test.

with deficient color perception for red and green. Each of these tests, however, fails occasionally to detect mild degrees of red-green deficiency. Misclassification of normal subjects as color-deficient is more likely to occur with the AO-HRR screening plates than with either the Ishihara or the Dvorine test.

3. A comparative analysis of the responses to the individual plates of each series indicates that, in order to detect borderline cases, certain plates of all three tests should be modified to make them more difficult for the color-deficient observer. The occasional misclassification of normal subjects by the AO-HRR test could best be reduced by an increase in the number of screening plates and the adoption of a less stringent passing score.

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Choroidal Detachment in the Surgical Treatment of Retinal Separation

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The literature on retinal detachment is extensive; therefore, it is surprising that there is a paucity of data concerning the fundamental changes induced in the choroid by treatment of this condition. For example, in the literature there are numerous reports which have concerned choroidal detachment occurring during the course of surgery on the anterior segment, but there are only a few references to its occurrence in operations for retinal detachment. Its incidence, pathogenesis, and significance have not been documented.

It is the purpose of this report to record the circumstances under which acute choroidal detachment was observed to develop in operations for retinal reattachment and to describe some experiments which were directed toward determination of the mechanisms involved. This study is one of a series of investigations directed toward obtaining a better understanding of the pathogenesis of retinal separation and of the principles underlying its successful treatment. Our two previous reports concerned the various types of diathermy and the reaction of the sclera to heat injury.* The next logical step seemed to be to investigate the reactions of the choroid both to heat injury and to other alterations, such as choroidal detachment induced in the surgical treatment of retinal separation.

The ophthalmoscopic picture of acute choroidal detachment in the human eye has been adequately described. Minor degrees of choroidal detachment cannot be recognized clinically, but large detachments can be distinguished without difficulty. Generally, the detachment is most pronounced in the equatorial region and anteriorly, where attachments of the choroid to the sclera are almost negligible. Typically, the elevation is brown, smooth, and relatively stable. The histologic picture of choroidal detachment also has been well described. The surface layers of the choroid are elevated by protein-rich fluid or gross blood, which largely accumulates in the outer layers and separates the epichoroidal fibers (Fig. 1). The choroidal vessels are dilated, and local areas of rupture sometimes can be found. In reality, "choroidal detachments" are due to edema or hemorrhage or both separating the fibers, rather than elevating the choroid as a unified membrane from the sclera.

The pathogenesis of choroidal detachment occurring during the course of anterior segment surgery is disputed; however, acute hypotony has been noted to be a common precipitating factor. Thus, O'Brien observed varying degrees of choroidal detachment to be present at the conclusion of nearly all intracapsular cataract operations in which the incision had been made with the Graefe knife.[3] The magnitude of drop in ocular ten-

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From the Department of Ophthalmology, University of Oregon Medical School.

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sion also has seemed a factor. Choroidal detachment, and even expulsive hemorrhage, due to rupture of the choroidal vessels, is particularly prone to occur when a high ocular tension is reduced abruptly.

It now is generally accepted that the protein-rich fluid or blood originates from the choroidal vessels; Vilstrup's recent studies of the choroidal circulation indicate why this occurs.[4] She noted that the hydrostatic pressure in the choroid normally is high in the arterial side of the system. Furthermore, the vessels of the arterial side are capable of dilating and carrying an increased volume of blood. In contrast, the capillary and venous systems of the chorid are relatively inflexible and constantly carry a near-capacity volume. Such a system, favoring extravascular diffusion on the capillary and venous side, would be ideal to meet the nutritional needs of the avascular outer layers of the retina; however, an acute dilatation of the choroidal arterioles would overburden the already maximally loaded venous and capillary systems and favor the transudation of protein-rich fluid into the choroid, as well as through Bruch's membrane. Vilstrup was able to demonstrate this by intracarotid injections of histamine. A similar acute choroidal dilatation with acute overloading of the venous and capillary systems could be expected to develop with any sudden drop in ocular tension. Then there would be decreased support of the choroidal vessels by hydrostatic pressure of the intraocular fluids.

There is evidence that mechanical indentation of the sclera also may contribute to the separation of the choroidal fibers in a soft eye. In this respect, Dellaporta noted acute choroidal detachment to occur in the dog's eye when the aqueous was aspirated and a scleral infolding operation was performed.[5] The choroidal detachment largely was localized to the area of the infolding and lasted two to four days. It would seem that the choroid does not readily adapt to changes in scleral curvature.

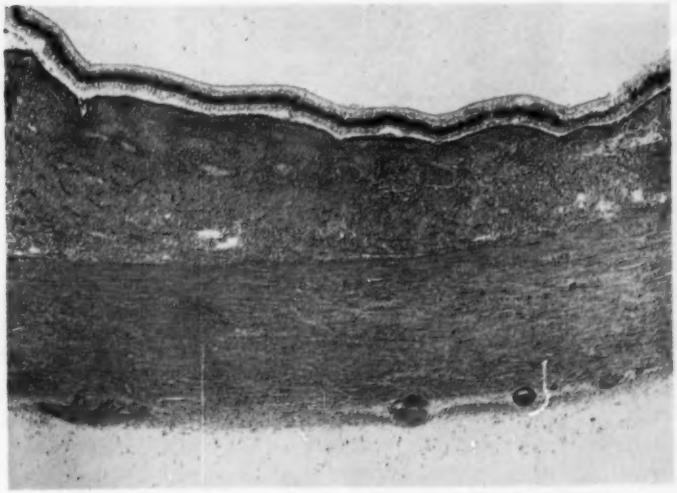

Fig. 1.—Choroidal detachment in a human eye. The retina and Bruch's membrane are elevated by protein-rich fluid and hemorrhage separating the choroidal fibers, particularly the outer layers. Reduced to about 65% of mag. × 53.

We have had the opportunity to study histologically the reaction of the choroid in the human eye six weeks after scleral resection. The choroid had undergone some contraction to fit the new and flatter scleral curvature, but folds still were evident (Fig. 2). The same reaction often is noted in many atrophic eyes with over-all decrease in the diameter of the globe; that is, the choroid is capable of some contraction when not under tension, but it is not a highly elastic membrane in spite of the presence of elastic fibers in both Bruch's membrane and the choroid.

Considering these observations, acute choroidal detachment occurring as an immediate effect of surgery for retinal detachment might be expected to occur in association with operations in which the scleral curvature was flattened and hypotony was created by release of considerable subretinal fluid; however, the possibility has received only passing notice in the literature. For this reason, one of us (K. C. S.) systemically studied the fundus for evidences of choroidal detachment at the conclusion of 32 consecutive operations in patients with retinal detachments. In 18 eyes scleral imbrications were performed.† In these procedures a deep scleral incision was made and undermined anteriorly and posteriorly. The outer layers then were overlapped after diathermy was applied to the exposed deeper layers. Some infolding of the deeper layers of the sclera and the choroid necessarily was created in the equatorial region of the globe. In all cases considerable subretinal fluid was removed. Extensive choroidal detachment was noted in 15 of the 18 patients. In contrast, choroidal detachment was noted in only three out of nine patients who were treated by scleral diathermy and released of subretinal fluid without scleroplasty. In the three eyes which developed choroidal detachment, hypotony was present preoperatively, and some shrinkage of the sclera occurred with the applications of diathermy.

Finally, there were five patients in whom diathermy was applied either to the surface of the sclera with a ball electrode or with partially penetrating needle electrodes, but no subretinal fluid was removed. In none of these five cases was shrinkage of the sclera noted, and no choroidal detachment was observed.

In summary (Table), a choroidal detachment was not noted by ophthalmoscopic study in eyes to which diathermy was applied when the ocular tension was normal or elevated. Hypotony was present in all eyes in which choroidal detachment developed; however, it was not the sole causative factor. In every case of gross detachment of the choroid there was, in addition to hypotony,

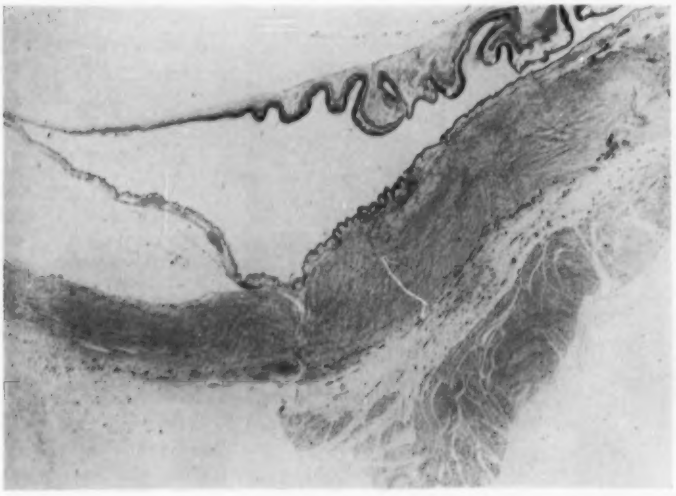

Fig. 2.—Scleral resection six weeks after operation in the human eye. The choroid is adherent to the healing scleral wound but is thrown into folds on either side of the incision. The choroid has not contracted to fit the new and flatter curvature of the sclera. Reduced to about 65% of mag. ×27.

Data on Thirty-Two Operations for Retinal Detachment

Procedure	No. of Eyes	Choroidal Detachment
Scleral imbrication and diathermy..	18	15
Diathermy & removal of subretinal fluid	9	3
Nonperforating diathermy.....	5	0
Total.....	32	18

† Swan, K. C., in discussion on Dellaporta.[5]

a flattening of the sclera, induced either by heat shrinkage or by imbrication of the outer lamellae of the sclera. When both these factors, scleral flattening and hypotony, were present, choroidal detachment developed in a high percentage of cases.

These clinical observations were supplemented with experiments on human and dog eyes. In previous publications we have reported the application of diathermy to viable human eyes which were to be enucleated for various disease processes.‡ By this means, the immediate effects of diathermy could be studied histologically and correlated with clinical observations. The sclera was exposed during the course of the enucleation, and diathermy was applied with various types of apparatus, electrodes, and currents, primarily to determine the effects of various types upon the sclera. In the course of these experiments, we noted that it was possible to induce a marked shrinkage of the sclera with minimal focal reaction if two conditions were established. First, it was necessary to create hypotony by the removal of the aqueous or vitreous. Then a ball electrode and low-amperage current were required to produce a diffuse heating of the surface layers of the sclera with minimal damage to the deeper structures.

In two human eyes choroidal detachment was produced when the surface layers of the sclera were shrunken by diathermy application made in the presence of hypotony, created by removal of the aqueous. In a third eye, the sclera, choroid, and retina were perforated by a needle electrode at the superior equator. There was some bleeding from the wound, as well as escape of considerable fluid vitreous. As a result, the eye was mushy-soft. It was evident that the large choroidal vessel had been perforated; so no further applications of diathermy were made. Gross inspection and histologic study of the enucleated eye revealed massive choroidal hemorrhage and detachment with almost no bleeding into the vitreous (Fig. 3). It was probable that, if there had been a large wound in the eye, the clinical picture of expulsive choroidal hemorrhage would have been produced.

Experiments also were conducted in dog eyes. Under general anesthesia, the superior half of the globe of these animals was exposed by reflecting the superior rectus muscle. By use of the superior oblique attachment as a landmark, diathermy applications could be localized to the same area in a number of animals. Before maximal shrinkage could be produced, it was necessary to create hypotony by paracentesis and removal of the aqueous. Extensive shrinkage of the surface layers of the sclera with minimal focal damage then could be produced consistently by use of a 4 mm. ball electrode and a low-amperage, vacuum-tube-generated current. Massive elevation of the choroid by protein-rich fluid and blood repeatedly could be obtained by shrinking the surface layers of the sclera with diathermy. In these eyes extensive choroidal detachment extended all around the globe and also involved the ciliary body (Fig. 4). In some eyes a smaller electrode and a greater amount of current were used to produce focal heat injuries extend-

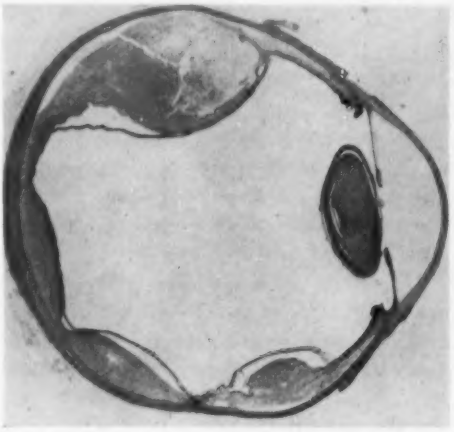

Fig. 3.—Massive choroidal hemorrhage induced by scleral perforation with a needle electrode. A high-amperage, vacuum-tube-generated current was applied below, at the equator, immediately after paracentesis but before enucleation. Enucleation was indicated for relief of pain from a blind glaucomatous eye.

‡ References 1 and 2.

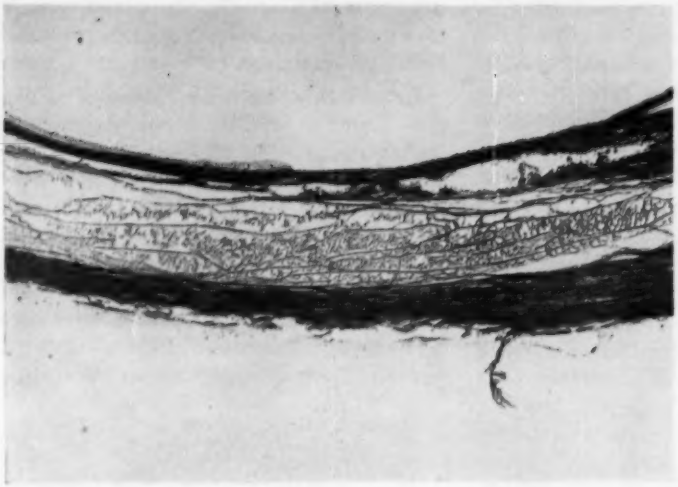

Fig. 4.—Ora serrata in the dog eye. Massive edema and hemorrhage separating the outer fibers of the choroid and ciliary body. Reduced to about 65% of mag. × 55.

ing completely through the ocular coats. In these eyes the choroid was detached except at the point of diathermy application; there the choroid was coagulated along with the sclera. The retina was thrown into folds (Fig. 5).

It will be necessary to review a larger series of cases, as well as to conduct additional experiments, before the full significance of choroidal detachment as induced above can be determined; however, several aspects can be discussed on the basis of present knowledge. First, during the course of surgery, the surgeon must be able to differentiate between a developing choroidal detachment and a residual separation of the retina. The former would require no treatment and might even have beneficial effects by elevating the pigment epithelium into contact with the retina, whereas residual separation of the retina would indicate the need for further surgical measures. Also, the presence of protein- and electrolyte-rich fluid between the choroidal fibers could be expected to affect profoundly the distribution of the diathermy current. The fluid would

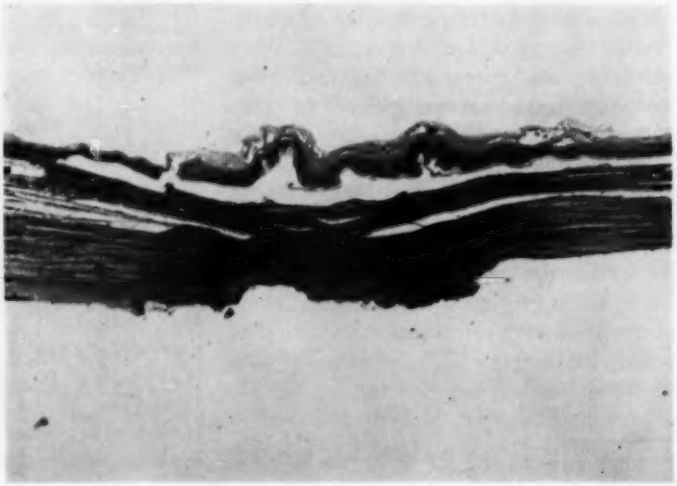

Fig. 5.—Region of ora serrata in dog eye. After paracentesis diathermy was applied to the sclera with a blunt-tipped electrode and a vacuum-tube-generated current of an intensity sufficient to produce a focal area of heat coagulation of the sclera, choroid, and retina. The coagulated sclera and choroid take a darker stain than the surrounding, untreated tissues. Detachment of the ciliary body can be seen to the left of the coagulum. Reduced to about 65% of mag. × 53.

tend to dissipate the current and reduce the focal heat injury to the choroid. It is conceivable, therefore, that choroidal detachment developing early in the course of retinal detachment surgery might significantly reduce the effectiveness of diathermy thereafter applied to the overlying sclera. We are conducting experiments to obtain additional information.

SUMMARY

Choroidal detachment frequently was found to develop during the course of operations for retinal reattachment if, in the presence of hypotony, the scleral curvature was altered by surgery or heat shrinkage. The causative roles of hypotony and flattening of the scleral curvature were substantiated by experiments conducted on dog eyes and on viable human eyes which were to be enucleated for other reasons. Hypotony was created by paracentesis, and the scleral curvature was flattened by application of low-amperage diathermy with a large ball electrode. It was possible to induce massive choroidal edema and hemorrhage.

Additional studies must be conducted before the full significance of choroidal detachment induced by surgery can be established. In the meantime it is imperative for surgeons performing scleroplasties to recognize and differentiate choroidal from residual retinal detachment.

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Selenium (Selsun) in the Treatment of Marginal Blepharitis

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INTRODUCTION

The widespread prevalence of blepharitis marginalis, described by Duke-Elder [1] as "a subacute or chronic inflammation of the margins of the lids," is well known. Its etiology is both complex and manifold and has not been conclusively defined.

Classically, this condition can be divided into two broad categories: (1) simple squamous blepharitis and (2) ulcerative blepharitis. The first reflects hyperemia, congestion, and edema of the lid margins with a consequent scaling of the lids. The latter involves the ciliary follicles and associated sebaceous glands of Zeis and sweat glands of Moll. At first, suppurative abscesses develop intrafollicularly, followed by more extensive destructive inflammation and subsequent scarring.

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The usual complications which follow include chronic conjunctivitis, hordeolum, chalazion, ectropion, entropion, trichiasis, and keratitis.

The principal causes to which blepharitis has been attributed * may be classified as those stemming from (1) predisposing factors, including eyestrain, metabolic disorder, vitamin deficiency, and heredity; (2) systemic infective disease; (3) contiguous conjunctival, lacrimal, or skin disease, and (4) localized marginal inflammatory disease, due to (*a*) seborrhea (sicca or oleosa), (*b*) Staphylococcus, or (*c*) Hemophilus duplex (Moraxella lacunata) in squamous blepharitis, and usually Staphylococcus in ulcerative blepharitis. Other agents of less importance locally include allergy and physical and chemical irritative factors.

Owing to the complicated etiologic nature of the disease, the treatment of blepharitis marginalis has been directed toward correcting (1) general constitutional factors and systemic disease, (2) associated conjunctival, lacrimal, and skin lesions, and (3) local sources of irritation; and toward providing specific local therapy. Local therapeutic measures range from epilation, mechanical removal of scales, glandular expression, x-ray therapy, and diathermy to the application of various soaps, lotions, oils, creams, and ointments containing antiseptics, antibiotics, and sulfonamides. The injection of autogenous Staphylococcus vaccine into the lids has likewise been employed.

Because of the successful treatment by Slinger and Hubbard [2] of seborrheic dermatitis of the scalp by the use of selenium sul-

* References 1 and 2.

fide, which result was subsequently duplicated by Slepyan,[4] Ayres and Ayres,[5] and others, it seemed worth while to apply the use of selenium sulfide ophthalmic ointment, in the form of a 0.5% suspension in a water-soluble jelly base, in a clinical trial in a series of unselected cases of marginalis blepharitis. While this study was being made, two reports were published by independent investigators on the favorable influence of this drug on the course of this disease.

Bahn[6] reported that 97% of his series of 100 cases of mild, moderate, and severe seborrheic blepharitis were "controlled" by the end of the fourth week by a combination treatment directed at treating both the scalp and the lids. The scalp was treated with nonalcoholic shampoos, followed by the use of selenium sulfide suspension. The lid treatment was divided into home and office care, the latter consisting of expression of lid glands and applications at regular intervals of selenium sulfide (Selsun) ophthalmic ointment, while the home treatment consisted of scrubbing the lids with antibiotic or sulfonamide ointment or with ammoniated mercury ointment over a similar period of time. Cohen[7] reported on 40 cases of marginal blepharitis of varying severity treated with a 25% solution of selenium sulfide in a Borofax base (10% boric acid in an ointment base) and used as an ophthalmic ointment, with applications every other night for four times, followed by a rest period of four to seven days. If the condition persisted, the course was repeated. He observed 92% of his cases cleared with this treatment but did not state the average length of time required for clearing. In both these studies there were no controls used.

In the present study we attempted to (1) determine the relative toxicity of the selenium sulfide ophthalmic preparation; (2) study the bacteriology and mycology of marginal blepharitis; (3) evaluate the merits of the use of this selenium sulfide ophthalmic preparation (0.5%) in blepharitis marginalis in a controlled clinical experiment, and (4) correlate the marginal blepharitis with seborrheic dermatitis of the scalp.

METHODS

A team composed of two ophthalmologists, a microbiologist, a dermatologist, and a biochemist was employed in this clinical investigation. Fifty-nine patients, including 29 males and 30 females, were included in the study. Their ages ranged from 2½ to 86 years, the median age of the entire group being 20.5 years.

Thirty-eight patients were given the selenium treatment, while 21 patients served as controls and were treated by the use of ammoniated mercury (5%). These subjects were all selected at random. Of the 38 selenium-treated patients, 18 were males and 20 females, while of the 21 ammoniated-mercury-treated patients, 11 were males and 10 females.

Twenty-four-hour specimens of urine were collected from eight patients at the start of the study for the purpose of determining the urinary selenium excretion as an indication of the extent of selenium absorption from topical administration of the test drug to the eyelids. The method employed for this analysis has been described by Sterner and Lidfeldt.[8]

Approximately 300 bacterial and mycotic cultures were made of the conjunctiva and seborrheic scales of the eyelids and the scalp taken from all patients. The methods used were as follows:

1. Collection of material from the conjunctival sac was made, with inoculation of thioglycollate broth. Subcultures were made on human blood agar plates, aerobically and anaerobically.
2. Gram stains were made of material from the conjunctiva.
3. Seborrheic scales from the eyelids and scalp were collected between sterile glass slides, cultured, and stained for fungi and bacteria.
4. Fungus cultures were made by placing the material on two Sabouraud slants, one of which was covered by a film of olive oil.

The blepharitis was classified according to its severity in three clinical categories: (1) mild, (2) moderate, and (3) severe. For purposes of this study, each eye was given an independent clinical classification and rated separately, thus allowing for different clinical categories for the eyes in the same subject. Accordingly, there were 117 eyes studied, as represented by the 60 patients of this study. Seventy-six eyes received the selenium treatment, while forty-one were accorded the ammoniated mercury treatment. There were 31 eyes with mild, 40 eyes with moderate, and 5 eyes with severe blepharitis in the selenium-treated group, as compared with 19 eyes with mild, 21 eyes with moderate, and 1 eye with severe blepharitis in the ammoniated-mercury-treated group.

Treatment schedules consisted of home treatment by the patient, who was instructed on the first visit to cleanse the lids thoroughly with warm water and a cotton swab or Q-tip, gently removing all scales from the lid borders of each eye. Each patient was then instructed to apply a matchhead-sized amount of ointment on a cotton swab, applicator, or Q-tip to each lid border. This, if correctly done, usually left an almost imperceptible film of ointment over each lid border along the lash line. This procedure was used by patients in both the test and the control group twice a day for four weeks, with weekly evaluations at the eye clinic. Treatment was then stopped for two weeks, at the end of which time each patient was requested to return for final evaluation and was questioned concerning any exacerbation or recurrence of blepharitis during this period of nontreatment.

In order to minimize any bias in the clinical grading of treatment progress, all clinical observers were without knowledge of the nature of the drug used by each patient being evaluated, and all drugs used were identified by code symbol only. All clinical progress was evaluated under the following categories: (1) no improvement; (2) slight improvement; (3) moderate improvement; (4) complete improvement; (5) condition worse. In the analytical phases of this study, however, it seemed expedient to combine categories of no improvement, slight improvement, and condition worse into one group, called "essentially no improvement," and categories of moderate improvement and complete improvement into a second group, called "improvement."

RESULTS

Biochemical Observations.—In Table 1 are shown urinary selenium excretion values, in micrograms, over a 24-hour collection period. These values ranged from a low of 17.0γ to a high of 36.9γ. The mean value was 24.5γ±2.8γ (S. E.).

Bacteriologic and Mycologic Observatoins.—Over 79% (227) of the bacteriologic isolates from the conjunctivae yielded a variety of Micrococcus pyogenes organisms. There were 30 sterile cultures. The bacteria identified are listed in Table 2. Fungus cultures of the conjunctiva yielded only one positive result, a species of Cryptococcus.

Table 1.—*Selenium in Urine Collected over Twenty-Four-Hour Period*

Patient	Urine Volume, Cc.	Selenium Excretion/24 Hr., γ
Control	1,550	21.6
1	1,675	23.8
2	600	24.0
3	1,250	37.5
4	450	17.0
5	1,075	20.2
6	875	13.8
7	450	18.0
8	1,230	36.9

Table 2.—*Bacteria Isolated from Conjunctivae*

Bacteria	Isolates
Micrococcus pyogenes var. albus, nonhemolytic	97
Micrococcus pyogenes var. albus, hemolytic	38
Micrococcus pyogenes var. aureus, nonhemolytic	79
Micrococcus pyogenes var. aureus, hemolytic	13
Alcaligenes faecalis	1
Proteus species	2
Bacillus species	4
Bacillus subtilis	10
Aerobic diphtheroids	9
Anaerobic diphtheroids	14
γ-streptococci	4
α-streptococci	7
Escherichia coli	4
Neisseria catarrhalis	1
Diplococcus pneumoniae	1
Clostridium perfringens	1
Sterile cultures	30

Cultures of seborrheic scales from both the scalp and the eyelids for bacteria yielded almost exclusively micrococci. Three cultures yielded a γ-Streptococcus. Mycologic studies of this material yielded 10 isolates of a lipophilic yeast-like organism. Since the identification of these fungi is very difficult,[9] no further attempt was made to identify these isolates. Three species of Cryptococcus were also isolated. They were not Cryptococcus neoformans, and no further attempt was made to identify them. Although fungus stains of the scales from the eyelids showed the presence of yeast-like organisms, none was identified.

Control cultures were made from the conjunctivae of 15 normal persons with no signs or symptoms of eye infections. The following organisms were isolated:

- Micrococcus pyogenes var. albus, hemolytic and nonhemolytic
- Micrococcus pyogenes var. aureus, hemolytic and nonhemolytic
- γ-streptococci
- α-streptococci
- Aerobic diphtheroids
- Micrococcus species

Two cultures were sterile for bacteria, and no fungi were isolated from any of these 15 subjects.

Clinical Observations. — Previous Treatment: Of the 60 patients studied, 16 (27%) had had previous treatment by an ophthalmologist, while 4 (7%) had been treated by a family physician. Forty (64%) stated that they had previously received no professional treatment. In terms of the total eyes studied, 31 (26%) of the total 117 eyes had been treated by an ophthalmologist; 8 (6%) had been treated by a family physician, while 78 (68%) had received no professional treatment.

Duration of Blepharitis: Of the total of 60 patients studied, 12, or 20%, stated that they had had blepharitis for less than one year. Twenty-nine, or 51% of the entire sixty patients, stated that they had had blepharitis for less than five years. Nineteen (32%) claimed to have had it for over five years, and ten (17%) were unaware of the presence of blepharitis until it had been pointed out to them in a routine clinic examination.

Previous Lid History: When the histories of previous lid conditions, including hordeolum, chalazion, conjunctivitis, or meibomianitis, were studied, it was revealed that 71, or 60%, of the eyes studied had had one or more of these conditions in the past, while 46, or 40% of the eyes, were associated with negative lid histories. Interestingly, for 74, or 63%, of the eyes studied there was an associated history of seborrheic dermatitis of the scalp, with or without accompanying involvement of other parts of the face. Forty-three, or 37%, of the eyes, had no history of seborrhea at all.

Associated Conditions: Eighty-one (69%) of the total eyes examined were found to be associated with a varying degree of conjunctivitis. Other associated conditions included dacryocystitis (one eye), chalazion (two eyes), and meibomianitis (three eyes). In 95 eyes (81%) the blepharitis was related to seborrheic dermatitis of the scalp, which was classified as seborrhea oleosa in 2 cases and as seborrhea sicca in 93 cases. Other skin conditions found were postaural seborrhea (17 eyes, or 15%) and nasolabial seborrhea (10 eyes, or 9%).

Classification: Clinical cases were classified as those of (1) squamous and (2) ulcerative blepharitis. The squamous type was further divided into (*a*) staphylococcic and (*b*) seborrheic. No Hemophilus duplex blepharitis was found in this study. There was also a miscellaneous (mixed) group.

Of 117 eyes, 104 (89%) had seborrheic squamous and 10 (8%) staphylococcic squamous blepharitis. Ulcerative types numbered two cases (2%), while one (1%) was in the mixed group (Table 3).

Treatment: The clinical results for all eyes treated, both the selenium-treated and the control preparations, can be found in Table 4.

TABLE 3.—*Clinical Types of Blepharitis in Eyes in Test and Control Groups*

	Selenium (Test)				Ammoniated Mercury (Control)				Total			
Type	Mild	Mod.	Sev.	Total	Mild	Mod.	Sev.	Total	Mild	Mod.	Sev.	Total
Squamous												
Staphylococcic	1	5	0	6	2	2	0	4	3	7	0	10
Seborrheic	30	35	3	68	17	18	1	36	47	53	4	104
Ulcerative	0	0	2	2	0	0	0	0	0	0	2	2
Mixed	0	0	0	0	0	1	0	1	0	1	0	1
Total	31	40	5	76	19	21	1	41	50	61	6	117

TABLE 4.—*Number of Eyes Improved in Test and Control Groups According to Severity of Blepharitis*

	Selenium (Test)				Ammoniated Mercury (Control)				Total			
Improvement	Mild	Mod.	Sev.	Total	Mild	Mod.	Sev.	Total	Mild	Mod.	Sev.	Total
Essentially unimproved	5	11	0	16	2	2	0	4	7	13	0	20
Improved	26	29	5	60	17	19	1	37	43	48	6	97
Total	31	40	5	76	19	21	1	41	50	61	6	117

Of 31 eyes with mild blepharitis treated with selenium, 26, or 84%, were essentially improved. Controls, consisting of 19 eyes, showed 17, or 89%, improved. In the moderate blepharitis cases, 29 of the 40 eyes, or 73%, treated with selenium showed improvement. The controls showed improvement in 19 of 21 eyes, or 90%.

Of the entire group of 76 eyes observed under selenium treatment, 2 were clinically worse at the end of the period of observation. These two were originally classified as having moderate seborrheic blepharitis.

All five eyes with severe blepharitis, as well as one control in this category, showed improvement.

In the series considered as a whole, 60 of the 76 eyes receiving selenium were improved, representing 79%, while 37, or 90%, of the 41 controls were improved. The difference in the results obtained between these two groups in this study in all categories described was not considered statistically significant according to the χ^2 tests of significance.

Table 5 contains a tabulation of maximal clinical improvement attained according to week of treatment. Of the entire group of 60 eyes improved by selenium treatment, 10, or 17%, had obtained maximum improvement by the end of the first week. By the end of the second week, 24, or 40%, had maximally improved. This is in contrast to the control group, in which 16, or 43%, of the 37 controls had maximally improved by the end of the first week and 18, or 49%, had improved by the end of the second week. By the end of the third week, 37, or 62%, of the treated eyes had improved, as against 32, or 86%, of the controls.

In the cases of moderate blepharitis, selenium-treated eyes which were improved by the first week numbered 5, or 17%, as against 12 controls, or 63%. By the end of the third week, 16 (55%) of the selenium-treated eyes had improved, as against 17 (89%) of the controls. In the cases of mild blepharitis, 5, or 19%, of the treated eyes had improved maximally by the first week, as against 4, or 24%, of the controls. By the end of the third week, 20, or 77%, of the selenium-treated eyes had obtained this maximal improvement, as compared with 14, or 82%, of the controls. Tests of significance of this study revealed no marked difference between the test and the control groups in all categories studied.

TABLE 5.—*Number of Eyes Improved in Test and Control Groups According to Week of Maximal Improvement and Severity of Blepharitis*

Week of Maximal Improvement	Selenium (Test)				Ammoniated Mercury (Control)				Total			
	Mild	Mod.	Sev.	Total	Mild	Mod.	Sev.	Total	Mild	Mod.	Sev.	Total
1	5	5	0	10	4	12	0	16	9	17	0	26
2	8	5	1	14	2	0	0	2	10	5	1	16
3	7	6	0	13	8	5	1	14	15	11	1	27
4	6	13	4	23	3	2	0	5	9	15	4	28
Total	26	29	5	60	17	19	1	37	43	48	6	97

Seborrheic Dermatitis of Scalp: There were 49 in the entire group of 60 patients in this study who had a concomitant seborrheic dermatitis of the scalp. This represented 82±5% (S. E.). On the other hand, there were 11 persons who had no seborrhea dermatitis of the scalp, representing 18±5% (S. E.). In the test group, there was a total of 34 patients, or 87%, who had seborrhea, as compared with 15, or 71%, with scalp seborrhea in the control group, a difference of no statistical significance (16±11.3; S.E. of difference) (Table 6).

Of the 49 cases of clinical scalp dermatitis, there were 32 (65%) which were classified as mild, 15 (31%) as moderate, and 2 (4%) as severe. The distributions of patients according to severity of scalp dermatitis in both the test (selenium) and the control (ammoniated mercury) group were similar.

TABLE 6.—*Severity of Seborrheic Dermatitis of Scalp in Patients in Test and Control Groups*

Severity of Scalp Seborrhea	Selenium (Test) Group	Ammoniated Mercury (Control) Group	Total
Mild	23	9	32
Moderate	10	5	15
Severe	1	1	2
No scalp seborrhea	5	6	11
Total	39	21	60

There were 23, or 68%, mild cases in the test group, as compared with 9, or 60%, in the control group; 10, or 29%, moderate cases in the test group, as against 5, or 33%, in the control group, and 1, or 3%, in the severe category in the test group, as against 1, or 7%, in the control group.

Of the 62 eyes associated with mild scalp dermatitis, 23, or 37%, had mild blepharitis, while 35 (56%) had moderate blepharitis and 4 (7%) had severe blepharitis. Of the total of 29 eyes associated with moderate scalp dermatitis, 16, or 55%, had mild blepharitis, 11, or 45%, had moderate blepharitis, and 2 had severe blepharitis.

Of the 4 eyes associated with severe scalp dermatitis, 1 (25%) had mild blepharitis and 3 (75%) had moderate blepharitis (Table 7).

No significant correlation could be drawn between severity of scalp seborrhea and marginal blepharitis at the onset and during treatment.

COMMENT

Toxicity.—Two patients receiving selenium treatments developed keratitis, accompanied by conjunctivitis with erythematous and swollen lids. These cleared on cessation of the drug. Both had moderate seborrheic blepharitis, and both developed these complications during the second week of treatment with selenium. This experience is similar to that reported by Bahn,[6] who described similar complications in three cases, using a 0.5% selenium sulfide ophthalmic ointment also. No complications were experienced by any of the control patients receiving ammoniated mercury treatment.

Bacteriology.—The majority of the microorganisms isolated during this study may be considered normal flora, although it is readily recognized that these same organisms may be the etiologic agent in an acute infection of the eye. Trevor-Roper [10] stated that approximately 50% of normal conjunctivae are sterile. Among the nonpathogenic organisms which he recovered from conjunctivae that were not sterile, over 80% were micrococci, of which a fifth were M. pyogenes var. aureus. Diphtheroids made up about 30% of the organisms isolated, and barely 1% were pneumococci and streptococci. In this study, approximately 85% of the conjunctivae cultured were not sterile. Seventy-nine per cent yielded micrococci, of which over 30% were M. pyogenes var. aureus.

Winkler and Gason [11] referred to Gram-negative bacilli in certain eye infections as "opportunists." It is interesting to note that four cultures in this study revealed E. coli, and two contained Proteus species and Alcaligenes faecalis.

Hughes [12] presented a list of microorganisms which were isolated from conjunctivitis. Included among these organisms were micrococci, streptococci, pneumococci, N. catarrhalis, E. coli, B. subtilis, and Clostridium welchii.

From the bacteriologic studies conducted in this study, it is difficult, if not impossible, to distinguish in most instances between

TABLE 7.—*Severity of Seborrhea Dermatitis of Scalp According to Severity of Blepharitis in Eyes in Test and Control Groups*

Severity of Scalp Seborrhea	Selenium (Test)				Ammoniated Mercury (Control)				Total			
	Mild	Mod.	Sev.	Total	Mild	Mod.	Sev.	Total	Mild	Mod.	Sev.	Total
Mild	16	25	3	44	7	10	1	18	23	35	4	62
Moderate	12	6	2	20	4	5	0	9	16	11	2	29
Severe	0	2	0	2	1	1	0	2	1	3	0	4
No scalp seborrhea	3	7	0	10	7	5	0	12	10	12	0	22
Total	31	40	5	76	19	21	1	41	50	61	6	117

"normal flora" and "pathogenic flora" of the eye. Many of the organisms isolated are normal skin flora and are also air-borne contaminants. When they are isolated under pathologic conditions, they are probably contaminants or "opportunists." It would be difficult to tell which was the actual situation.

From the mycologic studies presented, it would appear that fungi were rarely present in the conjunctivae. The species of cryptococci isolated were not recognized pathogens and were most likely contaminants from the air or skin. Approximately 30% of the scales removed from the eyelids and stained for fungi revealed the presence of yeast-like organisms, although all cultures were negative. Since Sabouraud's agar covered with olive oil was the only medium used, the failure to isolate fungi from these scales may be due to a nutritional factor. Gordon [9] and Benham [13] have shown that the lipophilic yeast-like organisms vary in their requirement for growth.

In comparison, Gots, Thygeson, and Waisman [14] reported the occurrence of Pityrosporum ovale, a lipophilic fungus, in scrapings from 100% of their 143 cases of clinically recognized seborrheic dermatitis of the eyebrows and eyelids. However, their attempts at culture, using wort agar with oleic acid, were not as successful.

Throughout this study there was no evidence of any significant changes in the microbiology of the eyes of patients with blepharitis before, during, or after treatment, regardless of the treatment received. There was no evidence presented that any of the micro-organisms isolated served as an etiologic agent of this disease, nor was there a disappearance of these organisms as the patient's clinical blepharitis improved.

Treatment.—It would have been desirable for this study to have included a larger number of patients. Originally, 20 additional patients had been interviewed and placed in either test or control categories. However, they were omitted from the study because of failure either to perform the treatments regularly as outlined or to return for their scheduled clinic evaluations.

Six known recurrences within a year of successful treatment with selenium were cleared by the fourth week with a repetition of the same treatment. How many other recurrences in this same treated group were not brought to the attention of the eye clinic is unknown.

It should be noted that Thygeson,[2] among others, has advocated combination treatments for marginal blepharitis. In seborrheic blepharitis he recommended Meibomian gland expression, epilation of diseased lashes, mechanical cleansing of lid margins, and associated treatment of the seborrheic scalp, brows, and external ears, in addition to local use of various ophthalmic ointments. In staphylococcic blepharitis he has advocated, in addition to other measures, anti-Staphylococcus treatment with Staphylococcus toxoid. In the light of the multiple possibilities for influencing the treatment of blepharitis favorably, it was considered expedient to employ only the test drug which could be evaluated against its control under similar therapeutic conditions. Owing to the small number of cases available, no attempt was made to employ the combination therapeutic approach to this problem.

Because of the wide variety of therapeutic measures utilized by Bahn [6] in his report, in addition to the use of selenium ophthalmic ointment (i. e., refraction; Meibomian gland expression; home treatment with antibiotic or sulfonamide ointment or ammoniated mercury ointment, and scalp treatment with selenium suspension), it is difficult to assess the true role of the selenium ophthalmic ointment in his 97% of successes at the end of the fourth week.

Cohen [7] reported that 92% of his cases cleared with apparently topical treatment alone. No time of clearing is given, although the period of observation varied from 3 to 12 months.

The results of the present study do not compare favorably with those of Cohen, particularly in the light of successes experienced by controls treated with ammoniated mercury. Successes in the selenium-treated group of 76 eyes constituted 79%±4.7%

(S. E.), while those in the control group, of 41 eyes, comprised 90%±4.7% (S. E.). The results of this study likewise produced no evidence that improvement experienced by selenium-treated patients was obtained more quickly than by those in the control group.

While 49 of the 60 patients studied, or 82%±5% (S.E.), had an accompanying seborrheic dermatitis of the scalp, no correlation could be produced between the severity of the scalp seborrhea and that of the seborrheic blepharitis before, during, and after treatment.

SUMMARY

Biochemical and clinical studies with selenium (Selsun) sulfide ophthalmic ointment (0.5%) indicate that this preparation is relatively nontoxic when applied to the eyelid margins.

The mean urinary excretion value for selenium over a 24-hour collection period was 24.5γ±2.8γ (S. E.), which is within normal limits. Of 76 eyes receiving selenium, 4 developed transient keratitis and conjunctivitis, which were relieved by cessation of the drug. No local complications were observed in the control eyes.

No evidence was presented that would indicate that the etiology of blepharitis was a specific infectious agent or that the treatment given these patients affected the microbiologic flora of the eyes.

The results for 76 eyes with marginal blepharitis treated with selenium ophthalmic ointment do not differ significantly from those for control eyes, numbering 41, treated with ammoniated mercury ointment. Successes in the selenium group were 79%±4.7% (S. E.), as against 90%±4.7% (S. E.) in the control group by the fourth week.

Forty-nine, or 82.5%±5% (S. E.), of the entire group of 60 patients with marginal blepharitis had concomitant seborrheic dermatitis of the scalp. No correlation could be produced between the severity of the scalp seborrhea and the severity of the blepharitis.

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Retinal Breaks in Eye Bank Eyes

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This work is reported to augment the accumulating information on etiology and management of retinal detachment. It reports a high incidence of retinal breaks seen in presumably normal eyes. It is the first report of subclinical retinal breaks examined ophthalmoscopically in unfixed specimens, followed by histological study. It reports horseshoe, as well as round, breaks seen in presumably normal eyes.

TECHNIQUE

Eye bank eyes were used. They were presumably normal eyes and had been refrigerated in saline from two and a half days to two weeks before examination. A total of 11 eyes was studied. The eye was placed on an examining stand. The iris and lens were removed. A contact glass was placed over the opening in the cornea and the space between the glass and the vitreous face filled with saline. Indirect ophthalmoscopy, with the Schepens instrument and technique,* was employed to examine the fundus, and drawings were made when significant pathology was found. There was retinal detachment in all the eyes, which increased in proportion to the amount of time the eyes had been opened. There was almost invariably an equatorial detachment and/or fold corresponding to the pressure transmitted from the edges of the holder. That portion of the retina at and near the ora was the last to become detached, and it was here that the normal anatomy was best preserved. After fixation, the pathological areas were examined under the dissecting microscope; at this stage the retinas appeared fairly well back in position, the artifactual detachments having grossly subsided. Finally, histological sections of the grossly pathological areas were studied.

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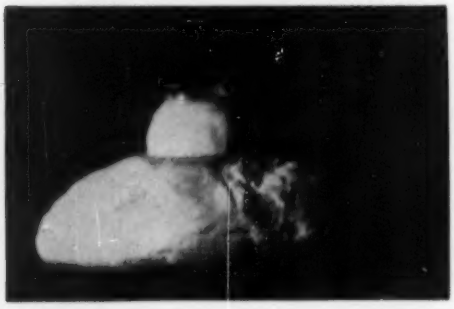
Fig. 1.—Eye bank eye: mounted in clay holder; cornea, iris, and lens removed; contact glass in place, ready for indirect ophthalmoscopy with scleral pressure.



FINDINGS OF SIGNIFICANCE

EYE 1.—*Ophthalmoscopy.*—A horseshoe-shaped break at 12 o'clock with a tiny break to the nasal side was seen.

After Fixation.—The cut section showed a retinal break, 1 mm. wide by 1.5 mm. long, with its operculum folded back toward the ora and fixed there by the contracted vitreous attached to its peak. There was a small break at the lateral anterior corner. This pathology was bounded on two sides by a branching vessel.

Histopathology.—A retinal detachment extends almost to the ora and backward to the posterior pole. It is not possible to determine how much of the detachment is artifactual. Between the ora and the equator there is a complete defect in the retina, which is totally dissimilar to other artifactual breaks seen toward the posterior pole. The free end of the broken retina on the ora side is folded back toward the ora serrata. Its internal limiting membrane throughout is in contact with the vitreous structure, and at its broken tip, where it fuses with the outer limiting membrane, there are about six large glial

* References 1 and 2.

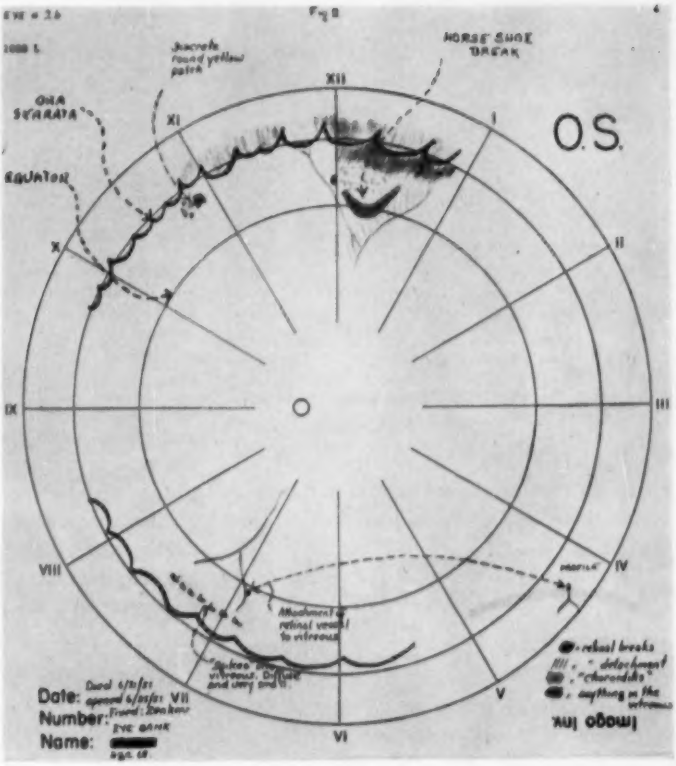


Fig. 2.—Retinal breaks and other pathological areas charted on retinal diagram.

cells pulled out of their normal architectural axis in the direction of the ora.

In the peripheral (ora) part of the broken and detached retina there is extensive cystic degeneration. There is fair preservation of the retinal architecture, except near the broken end (peripheral), where the rods and cones are almost gone and the cysts in the internuclear layer push its components aside. There are almost no ganglion cells, and the nerve fiber layer shows a good deal of autolysis. Some sections show a definite scalloped or tented internal limiting membrane at the peripheral broken end. Vitreous

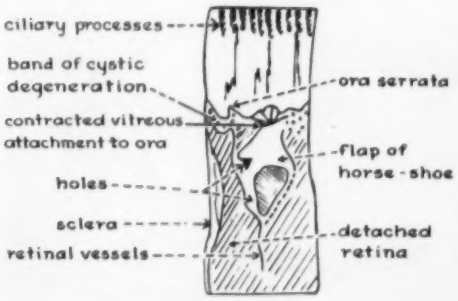
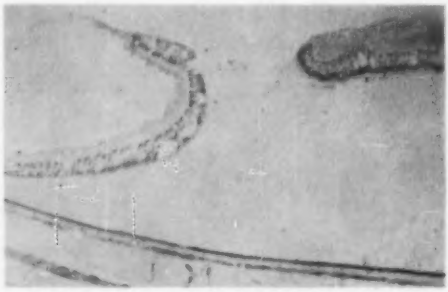


Fig. 3.—Horseshoe break after fixation, seen with dissecting microscope.

Fig. 4.—Horseshoe break. Vitreous adherent to the extremity of the flap, pulling it toward the ora serrata.



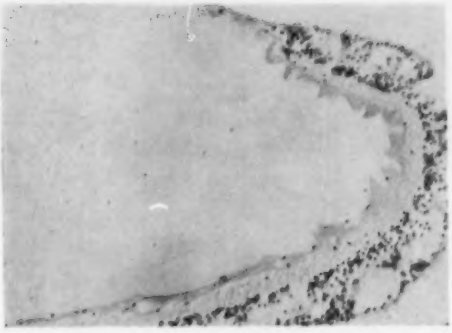


Fig. 5.—High-power photograph of horseshoe flap having (*a*) vitreous strands pulling internal limiting membrane into peaks and (*b*) extensive cystic degeneration.

Fig. 6.—Central side of horseshoe break, showing (*a*) rounded end without vitreous connection, (*b*) cystic degeneration, and (*c*) beginning separation of distal piece.

strands, more heavily stained than their surrounding vitreous tissue, connect to the peaks of the tents, appearing to pull them toward the ora serrata.

The other broken end of the retina (central, or disc, side) is rounded, with fair preservation of the normal architecture, except that the rod and cone layer is badly preserved and is nonexistent on the extreme end. Here the cells of the nuclear layers swing around to fuse with the nerve fiber layer. In contrast to the peripheral broken end, there is no evidence of traction from the vitreous. Some areas in the centrally broken end show cystic degeneration. The central broken end shows

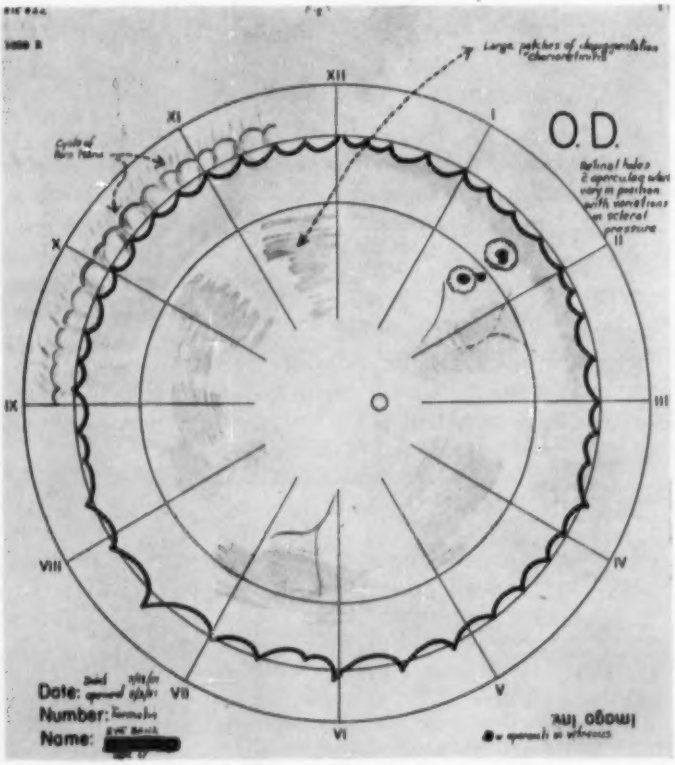


Fig. 7.—Two round holes with opercula.

Fig. 8.—Retinal photograph of two round holes with opercula almost directly over the holes.

a large vessel near its edge, perhaps indicating the supporting function of the retinal vessels as a scaffolding for the more delicate retinal tissue. Not far from the break there is an apparent partial division in the continuity of the nerve fiber layer, which, added to the more deeply penetrating cysts opposite this area, gives the impression that this piece might have broken out, causing a round hole with operculum rather than a horseshoe.

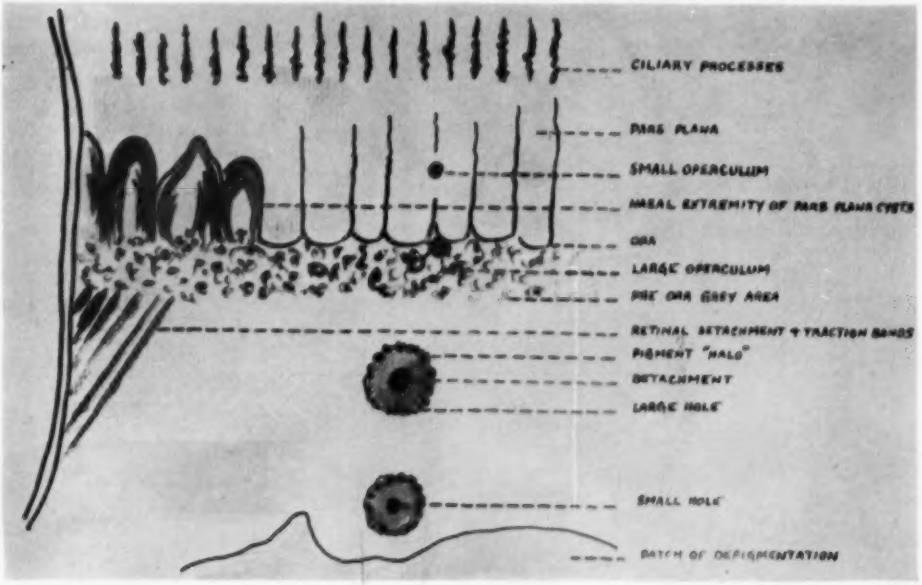
Eye 2.—*Ophthalmoscopy.*—There were two round retinal holes, with round opercula. The latter varied in position with variations in scleral pressure in their vicinity. The holes were clear-cut, surrounded by a rim of detached retina, which was bordered by a halo of fine choroidal pigmentation.

After Fixation.—Examination with the dissecting microscope showed the holes as they appeared by ophthalmoscopy. The remaining vitreous was a thin, clear, regular layer overlying the area anterior to the preora region of cystic degeneration. The two opercula were on the outer surface of this sheet of vitreous, in line with the holes, but pulled up over the pars plana.

Traction on the vitreous showed it to be attached posteriorly over the width of the area of cystic degeneration and anteriorly to the posterior extremities of the ciliary processes.

Eye 3.—*Ophthalmoscopy.*—This showed a horseshoe break and a round hole with operculum. The operculum of the horseshoe break seen in profile stuck out into the vitre-

Fig. 9.—Diagrammatic sketch of round holes and retracted opercula after fixation.



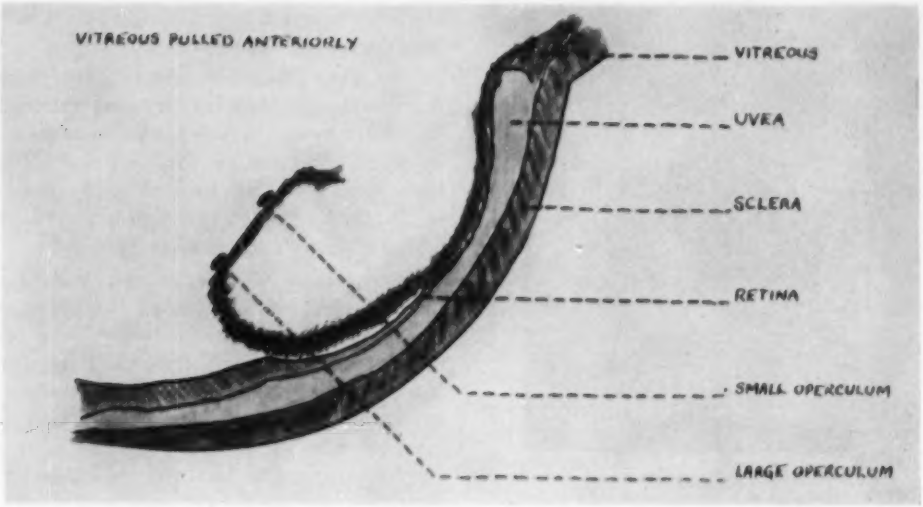


Fig. 10.—Diagrammatic sketch of cross section of round-hole opercula after fixation, illustrating the posterior and anterior attachments of the vitreous and the retracted opercula.

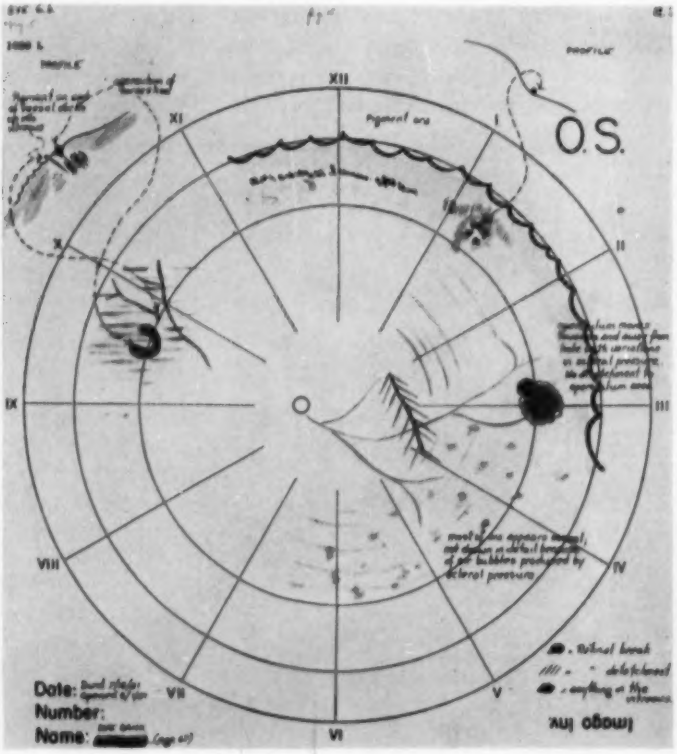


Fig. 11.—Horseshoe break and round hole, charted on retina diagram.

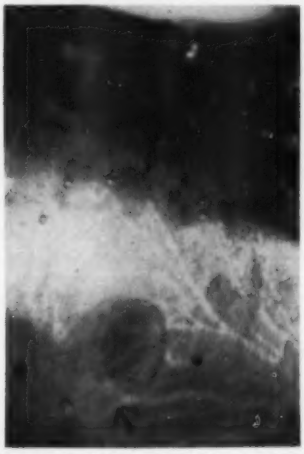


Fig. 12.—Retinal photograph showing round hole with border of detached retina, surrounded by halo of pigmentation. Operculum is indicated by arrow.

ous. The operculum of the round hole moved like a kite on a string with variations in scleral pressure.

After Fixation.—The round hole corresponded to its ophthalmoscopic appearance, being clear-cut, surrounded by a rim of detached retina, which was bordered by a halo of choroidal pigment. Attached to the vitreous, lying over the band of retinal cystic degeneration, was the operculum. It appeared to be fixed at its center, allowing its edges to curl up all around. The horseshoe tear was destroyed, owing to technical difficulties.

Histopathology.—These sections show a round hole with its operculum appearing in other sections. The retinal broken ends are rounded and slightly bulbous. The various layers lose their identity and fuse with the bulbous mass. The rods and cones are lost, and the external and internal nuclear layer cells are very sparsely represented at the

Fig. 13.—Round hole with artifactual retinal detachment outside areas of increased pigmentation on choroid.

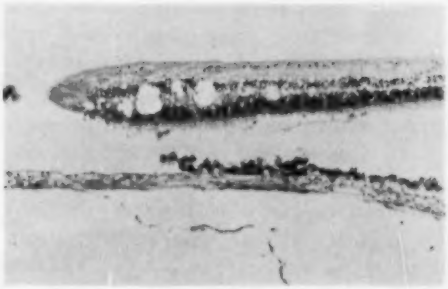


Fig. 14.—High-power view of one side of round hole, showing (*a*) bulbous end, (*b*) extensive cystic degeneration, and (*c*) proliferated pigment on choroid.

extreme ends, without any regular pattern. The ends are made up almost completely of supporting fibers, with a few glial cells. There are some moderately large cysts near the ends, corresponding to the bulbous swellings. There is considerable proliferation of the retinal pigment epithelium in a diameter larger than that of the hole. This corresponds to what was seen by ophthalmoscopy. The choroid is thin.

In those sections showing the operculum this structure appears as a round piece of retinal tissue. It is lying in contact with the inner limiting membrane and the vitreous face over the ora.

Résumé.—The retinas of 11 eye bank eyes were examined, before fixation, by indirect

Fig. 15.—Operculum belonging to round hole, pulled over pars plana by vitreous.

ophthalmoscopy and scleral indentation. Each of three of these presumably normal eyes were shown to have two retinal breaks.

There were two types of retinal breaks: a horseshoe tear, and a round hole with operculum. One eye had two round holes with opercula; another had one round hole with operculum and one horseshoe tear; the third had a horseshoe tear with another, small, break at its side. In both types vitreous adhesions were evident. The vitreous attachment associated with the round holes was a single strand attached to the operculum, while the edge of the hole itself was free from vitreous attachment and retraction. On the other hand, not only did the flap of the horseshoe tear have its extreme end pulled back by a vitreous adhesion, but the inner limiting membrane halfway to the ora serrata was tented up by multiple vitreous adhesions. The posterior edge of the horseshoe tear showed no evidence of vitreous attachment. The retina surrounding both types of breaks displayed extensive cystic degeneration on both sides of the breaks. The round holes showed evidence of retinochoroidal adhesions and pigment proliferation just peripheral to the free edge of the hole.

COMMENT

Hanssen [3] examined 37 myopic globes without retinal detachment and found breaks in 3 of them. He reported round holes without opercula. His pathological findings were similar to the round-hole microscopic sections in this work but contained no opercula. Teng and Katzin [4] examined by slit lamp 167 eye bank eyes, after fixation, finding 3 operculated holes and 1 organized hole.

Although this report is based on findings from a much smaller number of eyes than those of the authors cited, it seems significant, for the following reasons. It correlates ophthalmoscopy of the unfixed specimen with the microscopic and histological examination of the fixed material. The incidence of retinal breaks in the eyes examined is remarkably high in relation to that in the previously reported studies and, indeed, to what we believe is present clinically. The report contains studies of both horseshoe tears and round holes, seen in the same eye. There is a suggested similarity in the mechanism of formation of the two main types of retinal breaks; that is, some round holes may form in the same manner as horseshoe tears. The round hole may be formed when the manner and direction of vitreous traction and the conformity of the cystic degeneration are such that a complete piece of retina is removed, rather than being partially torn. With the removal of the complete piece, the vitreous traction on the retina in this area is relieved. In addition is the evidence that, as seen in this study, some retinal holes are surrounded by pigment proliferation, similar to that Wadsworth describes at demarcation lines.[5] Therefore, the danger of this type of break leading to clinical detachment of the retina may be less than the danger associated with a horseshoe tear.

SUMMARY

A new technique is described for the examination of retinas of enucleated eyes by indirect ophthalmoscopy. Horseshoe tears and round, operculated holes were found by ophthalmoscopy and examined histologically. Some reasons are suggested for believing that round operculated holes and horseshoe tears have a similar mechanism of formation.

Dr. C. L. Schepens originated the idea and technique for this study, and Dr. David Donaldson made the macroscopic retinal photographs.

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Allergic Granulomatous Angiitis Associated with Uveoscleritis and Papilledema

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Allergic granulomatous angiitis is one of the group of collagen diseases characterized by necrotizing lesions permeated with eosinophiles. The first clinical report of a similar disease was called periarteritis nodosa by von Rokitansky [1] in 1852. Kussmaul and Maier [2] described the pathological findings in 1866. Periarteritis nodosa, a systemic disease with ocular manifestations, was subdivided into three distinct pathological entities by Zeek.[3] One of these subdivisions, allergic granulomatous angiitis of the eye, has received little mention in the literature. An opportunity to study the eye of a patient with this disease presented itself at the Eno Laboratory of the New York Eye and Ear Infirmary in March, 1954, following enucleation at Lenox Hill Hospital.

REPORT OF A CASE

A woman of European origin, 67 years old, was admitted to New York Hospital in May, 1949, complaining of anorexia, weight loss, and severe weakness. Indistinct margins of the optic discs and enlargement of the liver were the only positive physical findings.

Positive laboratory findings were as follows:

White blood cells	20,000/cu. mm.
Circulating eosinophiles	5%-9%
Sternal-marrow eosinophiles	15%
Total blood proteins	5.8 mg./100 cc.
Albumin-globulin ratio	3.7/2.1
Sedimentation rate	50 mm. in one hr.
Trichinella precipitin test	Positive in 1/1280 dilution

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Aided by a grant from the Ophthalmological Foundation.

Biopsy (Figs. 1 and 2).—Sections from a biopsy specimen of striated muscle showed several arteries in which there was proliferation of the subintimal connective tissue, with infiltration of the adventitia and surrounding stroma by numerous lymphocytes and a moderate number of plasma cells. Isolated eosinophiles with bilobed nuclei were seen. In one vessel this perivascular infiltration measured 1 mm. in diameter. No thrombosed vessels were evident. A diagnosis of periarteritis of allergic type was made by George K. Higgins, pathologist of the New York Eye and Ear Infirmary.

Subsequent Course.—The patient's course subsequent to this was more specifically related to her eyes. In December, 1950, she visited the eye clinic at New York Hospital complaining of blurred vision and redness of the eyes. Her visual acuity was 20/30 in the right eye and 20/30 corrected in the left. A slight localized conjunctival inflammation was diagnosed as episcleritis. This was treated locally with cortisone and methapyrilene (Histadyl) until March, 1951, but showed no remarkable improvement.

In the same month, the right eye showed an aqueous flare and endothelial precipitations, with visual acuity reduced to 20/200 in the right eye and 20/30 corrected in the left eye. After local treatment with cortisone the right eye improved. By September, 1952, she had only a vitreous haze in the right eye, with normal disc margins in both eyes.

In October, 1953, the patient was seen at the eye clinic at Lenox Hill Hospital. Her visual acuity was light perception in the right eye and 20/30 corrected in the left. The right eye showed an enophthalmos, marked conjunctival injection, shallow anterior chamber, iris seclusion with posterior synechia, and a dense lenticular opacity. The intraocular tension was very soft to fingers, and light projection was faulty. The left eye was within normal limits except for marked blurring of the disc margins. The veins were not excessively dilated, and there were no hemorrhages on or near the disc. The visual field O. S. showed no peripheral constriction, and the blind spot measured 7×7 in. with a 6/1000 white test object. Because

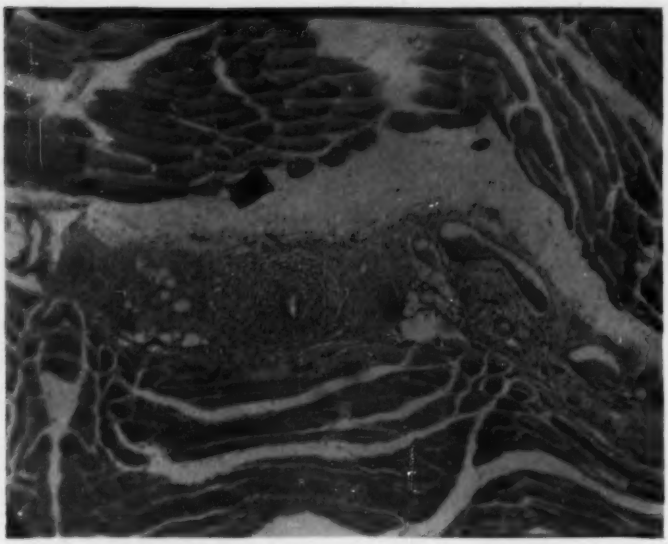

Fig. 1.—Biopsy specimen of deltoid muscle, showing vessels, some of which have marked adventitial infiltration by mononuclear cells. × 80.

of the possibility of increased intracranial pressure, she was admitted to the neurological service. Skull x-rays, EEG, and ventriculogram were normal. Spinal pressure was 230 mm. Hg, and the fluid was not unusual. Positive laboratory findings were 3% to 6% eosinophiles in the peripheral blood and a sedimentation rate of 65 mm. in one hour. Another muscle biopsy specimen from the right forearm showed no disease process.

During the hospitalization the patient complained of spells of "blacking-out" of vision. She was treated with various vasodilators, without beneficial results.

Early in January, 1954, she complained of a dull, annoying pain in the right eye, and it seemed advisable to enucleate the blind, painful eye. It was noted at surgery that all the tissues of the orbit were densely infiltrated and fibrotic. Pathological examination of the eye is reported as follows:

Microscopic Study.—Sections of the eye (Fig. 3), 21 × 22 mm., were somewhat pear-shaped and atrophic. They showed considerable inflammatory thickening of the sclera anterior to the equator. The ciliary body, iris, and choroid participated in this inflammation, and the anterior retina was

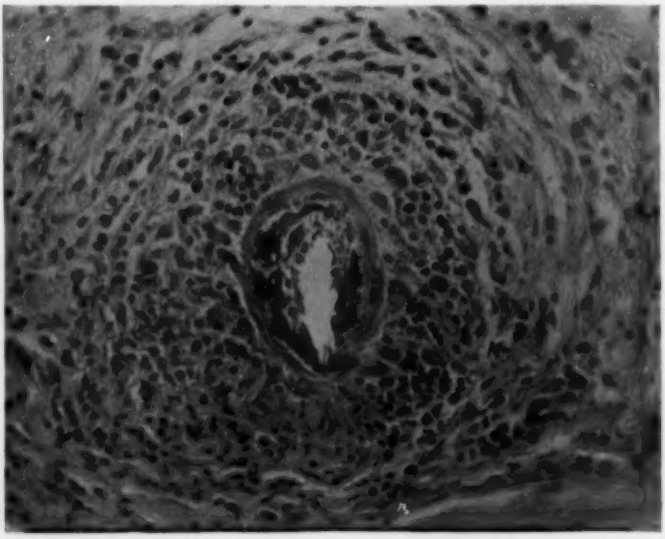

Fig. 2.—Higher-power view of vessel in Figure 1 (× 250). The intimal lining is prominent; the muscles are thick, but the chief changes are in the adventitia and consist of lymphocyte and plasma-cell infiltration.

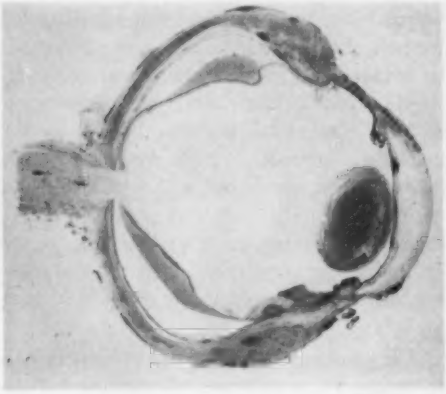

Fig. 3.—Section of globe showing massive involvement of iris, ciliary body, retina, and sclera. The optic nerve shows papilledema.

involved. A flat detachment of the retina extended from the ora serrata to the optic nerve on either side. The optic nerve was swollen as a result of hypotony and inflammation. Seclusion, with partial occlusion, of the pupil was present. The cortex of the lens was almost entirely cataractous. The vitreous contained fragments of inflammatory material, some of which had accumulated into strands attached to the retina and anterior hyaloid membrane.

A typical lesion (Fig. 4) extended from the corneal limbus to the equator of the globe on either side. It consisted of a necrotizing, granulomatous-like process composed of lymphocytes, plasma cells, atypical giant cells, and epithelioid cells. The sclera showed severe fibrinoid necrosis with foci of inflammatory cells, numerous eosinophiles undergoing necrosis, and granulomatous proliferation of epithelioid and giant cells. The smaller blood vessels showed closure by intimal thickening and perivascular infiltration (Fig. 3). The inflammation extended through the pars planum of the ciliary body into the vitreous. The iris contained foci of inflammation, in addition to generalized infiltration. The choroid shows diffuse inflammation and congestion.

The retina was swollen, detached, and necrotic in the periphery. The retinal vessels were almost entirely replaced by inflammatory reaction. Con-

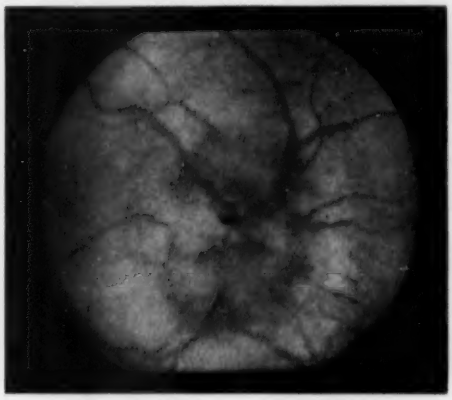

Fig. 5.—Photograph of left fundus, showing papilledema.

Fig. 4.—Section showing fibrinoid necrosis, inflammatory cells, and giant cells in sclera; × 80.

siderable gliosis extended to the optic nerve, which was inflamed and covered by a glial and fibrous mantle. Foci of inflammatory cells were seen on the disc and retina in some of the sections. A diagnosis of allergic granulomatous angiitis was made by one of us (B. F. P.).

Outcome.—At the time of her discharge, in February, 1954, the patient continued to show blurring of the disc margins O. S. (Fig. 5). Her vision O. S. was correctable to 20/30. Between February and May, 1954, she returned to the OPD, complaining of "black-outs" of vision. Examination showed no change, and the visual acuity remained 20/30 corrected.

The patient was seen at the New York Eye and Ear Infirmary on May 11, 1954, complaining of blurred vision O. S., at which time it was 20/50 corrected. Examination revealed papilledema. She was admitted, and with systemic cortisone therapy the papilledema subsided. On May 29, 1954, papilledema was not evident clinically and the corrected vision O. S. was 20/40. Her examination has not changed in the past 18 months.

COMMENT

In recent years the term "periarteritis nodosa" has given way to that of panarteritis, polyarteritis, or necrotizing angiitis, which more exactly describes a process involving all the coats of a blood vessel. The term "nodosa" has been eliminated, inasmuch as nodules are infrequently seen and cannot be listed among the diagnostic criteria.

In this category of collagen disorders there is fibrinoid degeneration of medium-sized and small vessels, including capillaries, throughout the body. Many vital systems, such as the liver, gastrointestinal tract, heart, lungs, and central nervous system, may be affected. In the eye this entity has caused papilledema, optic neuritis, retinal detachment, episcleritis, keratitis, uveitis, choroiditis and glaucoma.*

Zeek [3] found that pathological examination confirmed the clinical impression of several subdivisions of polyarteritis, which she outlined as follows:

1. *Polyarteritis.*—Polyarteritis is a chronic, progressive, necrotizing inflammatory disease of muscular-type arteries, which may extend to larger and smaller arteries and contiguous veins. Clinically, it is characterized by fever, polyneuritis, and "multiple systems disease." Pathologically, the basic lesion of polyarteritis involves the media of small and medium-sized arteries, arterioles, and sometimes veins. Segmental necrosis begins in the media and spreads through the inner elastic lamina. It is associated with leucocytic and eosinophilic infiltration of the vessel wall. As the process progresses, it tends to involve the interna. Plasma cells, lymphocytes, and macrophages may be seen in the areas of inflammation.

2. *Hypersensitivity Angiitis.*—Hypersensitivity angiitis is an acute, necrotizing inflammation in and around the smallest branches of blood vessels, both arterial and venous, of the viscera and connective tissues. Clinically the manifestations are those of hypersensitivity complicating the symptomatology of the infectious disease for which therapy had acted as an allergen. The course is rapidly progressive.

Pathologically, the process begins as a fibrinoid necrosis in the subendothelial ground substance of small vessels, rapidly producing necrosis of the entire vessel wall. There is a pleomorphic cellular reaction, often containing eosinophiles.

3. *Allergic Granulomatous Angiitis.*—Allergic granulomatous angiitis has been characterized by Churg and Strauss.[12] It is a clinical syndrome of severe asthma, fever, and hypereosinophilia, with vascular occlusive phenomena in various organ systems.

Small nodules close to blood vessels, and occurring in other collagen tissues, are found. These nodules consist of numerous necrotic eosinophiles, severe fibrinoid necrosis, and granulomatous proliferation of epithelioid and giant cells. The giant cells are of the typical mononucleated or multinucleated foreign body type and are frequently arranged around necrotic blood vessels or clusters of eosinophiles. Healing ensues, with fibrosis and scarring. The entity is usually chronic.

Two other disease entities are known but do not bear directly on this discussion. The first is rheumatic arteritis with Aschoff bodies in the myocardium and a clinical diag-

* References 4 to 11.

nosis of rheumatic fever. The other is temporal arteritis, an occlusive phenomenon, with fever, malaise, and pain along the course of the involved vessel.

ETIOLOGY

Polyarteritis is the only dyscrasia in the group of collagen disorders for which we have a due clue to its etiology. Laboratory research suggests that the lesions are manifestations of hypersensitivity. Rich [13] was the first in this country to produce vascular lesions in rabbits similar to polyarteritis by the intravenous injection of large doses of horse serum. Selye and Pentz [14] produced similar lesions in rats by a combination of unilateral nephrectomy, desoxycorticosterone acetate, and a high-sodium intake.

In humans, sulfonamides, mercurials, thiouracil, penicillin, iodine, arsenicals, and cortisone have been suggested as possible allergens. There is no consistent correlation, however, between the administration of these drugs and the appearance of polyarteritis. The allergic nature of polyarteritis is supported by the findings of Rackemann and Greene,[15] who reported 27 cases of polyarteritis occurring 1 to 25 years after a clinical diagnosis of bronchial asthma was made.

CASE COMMENT

The clinical course of the patient described in this case history was a chronic one, extending over a period of six years. Her symptoms of anorexia, weight loss, and severe weakness suggest a generalized process. There was no history of asthma, but the history of repeated bouts of "black-outs" of vision might indicate poor circulation somewhere along the optic pathways.

An enlarged liver and swelling of the optic nerve head point to "multiple systems disease," with the most prominent findings in the ocular tissues. Eosinophilia, both in the peripheral blood stream and in sternal marrow, a slight alteration of the A-G ratio, an elevated white blood cell count, and an increased sedimentation rate point to a chronic disease with allergic manifestations. The Trichinella precipitin test is known to give false-positive results in the presence of collagen disease.

Finally, the pathological reports of a muscle biopsy and sections of an enucleated globe showed lesions which fit the classical description of a necrotizing angiitic process. When the clinical, laboratory, and pathological findings are considered together, this case appears to meet the criteria necessary for a diagnosis of allergic granulomatous angiitis. A review of the literature reveals no other such description in ocular tissues.

SUMMARY

Allergic granulomatous angiitis occurring in ocular structures has received little mention in the literature. The opportunity to examine an enucleated globe which appeared to fit this diagnosis stimulated a brief review of the literature and the report of such a case.

The collagenous disease periarteritis nodosa is divided into several clinical and pathological entities, for which more exact terminology is suggested. These entities are polyarteritis, hypersensitivity angiitis, and allergic granulomatous angiitis. The possible role of allergy as an etiologic factor is discussed.

The case reported is that of a patient with a chronic history of papilledema progressing to atrophy of the globe. Laboratory and pathological findings fit the diagnosis of allergic granulomatous angiitis.

111 E. 59th St. (21).

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Use of Nylon Thread and Polyethylene Tubing in Nasolacrimal Duct Stenoses

Report of Sixteen Cases

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In view of the natural aversion of our people toward undergoing a major operation, such as dacryocystorhinostomy for the relief of epiphora, which to them is a trivial ailment, and more of a nuisance than a threat to life and vision, I was indeed happy to read of Veirs' successful use of the nylon rod and polyethylene tubing.[1]

Since then I have inserted nylon thread through the lower punctum and the inferior canaliculus and into the nasolacrimal duct, following exactly the method of Veirs, in 10 cases, and the polyethylene tubing in 6 cases, of nasolacrimal duct stenosis secondary to chronic, purulent dacryocystitis.

Recently, Oliver [2] inserted polyethylene tubing in 18 cases and concluded that the best results were achieved in cases of dacryocystitis with ectasia of the sac. Peyret [3] introduced a short polyethylene tube through the sac into the lacrimal duct, leaving it in situ, and claimed 9 entirely successful cases out of 10.

Contrary to the reports of Veirs, Oliver, and Peyret, in the present series of 10 cases with insertion of nylon, only 2 had patent ducts on irrigation, but still had tearing and chronic mucopurulent discharge with pressure on the sac. In two cases, there was less tearing, very little irrigating fluid passed into the nose, and plenty of mucopurulent discharge was expressed from the sac. In the remaining six cases the ducts were entirely blocked and unimproved.

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In the polyethylene group, of six cases, two showed less tearing, but still with mucopurulent discharge and very little irrigating fluid passing into the nose. In the remaining four cases the ducts were entirely blocked and unimproved.

According to Veirs, three to five days was sufficient time for the nylon or polyethylene tubing to be left in place to obtain a patent duct. Ample time, from one week to five months, has been allowed for the nylon and the tube to remain in the nasolacrimal duct, in the hope that epithelization of the passage would result in a permanently open duct. Leaving the nylon or the tube flush with the punctum or in the lower canaliculus was not tenable, as it invariably slid into the nasal cavity and became a source of danger in being aspirated or swallowed.

Prolonged intubation resulted in irritation and the appearance of granulation tissue at the punctum. All the 16 cases had persistent chronic conjunctivitis and discharge from the sac on pressure after the intubation.

NYLON THREAD

CASE 1.—Mrs. F. B., age 42. Nylon inserted July 7, 1952; removed after one week; no improvement.

CASE 2.—Mrs. E. A., age 37. Nylon inserted Sept. 10, 1953; removed after two weeks; no improvement. Reinserted March 17, 1954, and removed May 17 (two months); no improvement.

CASE 3.—Miss R. C., age 50. Nylon inserted in both nasolacrimal ducts July 22, 1953; removed Sept. 10 (1 month, 12 days). Bilateral irrigation; no fluid passed into the nose.

CASE 4.—Mrs. N. R., age 78; bilateral tearing. Nylon inserted right side, Dec. 23, 1953; removed Feb. 23, 1954 (two months); no improvement.

CASE 5.—Mrs. P. K., age 40. Nylon inserted left side March 19, 1954; removed May 17 (almost two months); duct patent on irrigation, but still with tearing and mucopurulent discharge.

CASE 6.—Mr. A. O., age 23. Nylon inserted March 27, 1954; removed May 1 (one month four days); duct closed. Reinserted June 15, 1954; removed July 10 (25 days); less tearing, with bloody mucus on irrigation and little fluid passed into the nose.

CASE 7.—Mrs. E. E., age 43. Nylon inserted left side May 8, 1954; removed June 7 (one month); duct patent on irrigation but still with tearing and chronic conjunctivitis.

CASE 8.—Mrs. G. L., age 47. Nylon inserted left side June 5, 1954; July 3, 1954, outer portion of nylon cut flush with punctum and rest left inside nasolacrimal duct. Patient seen last Jan. 21, 1955; less tearing but still plenty of mucus in the sac. Nylon spontaneously passed into nose and throat and expelled by mouth.

CASE 9.—Miss S. A., age 39. Nylon inserted Aug. 23, 1954; seen Dec. 20 (five months); punctum irritated, with granulation tissue; no improvement.

CASE 10.—Mr. J. E., age 30. Nylon inserted left side for one month; no improvement.

POLYETHYLENE TUBING

CASE 1.—Mr. J. T., age 46. Tube inserted Jan. 1, 1955, left side; removed Jan. 24 (24 days); duct still blocked. Larger tube inserted; removed Feb. 16 (22 days); no improvement. Dacryocystorhinostomy advised but refused.

CASE 2.—Mrs. C. R., age 32. Tube inserted March 10, 1955, right side; tube inserted, left side, March 17, and both removed March 26. Tearing less but discharge from sac still present.

CASE 3.—Mr. C. D., age 39. Tube inserted, left side, June 4, 1955; removed July 26 (one month); no improvement.

CASE 4.—Miss G. O., age 65. Tube inserted, right side, June 7, 1955; removed July 21 (1 month, 14 days); still tearing with granulation tissue at lower punctum. Dacryocystorhinostomy advised but refused.

CASE 5.—Mrs. P. M., age 33. Tube inserted, left side, June 8, 1955; removed July 23 (1 month, 15 days); slight improvement.

CASE 6.—Mrs. E. C., age 51. Tube inserted Aug. 2, 1955; removed Aug. 8 (six days); duct still blocked.

SUMMARY AND CONCLUSION

Of 16 cases of nasolacrimal duct stenosis secondary to purulent chronic dacryocystitis, nylon thread was used in 10 and polyethylene tubing in 6. The nylon and the polyethylene tube were left in situ from six days to five months. In all cases, after intubation, tearing persisted, with discharge from the lacrimal sac on pressure, accompanied by chronic conjunctivitis. The ducts were patent on irrigation in two cases, with little irrigating fluid passing into the nose in another two cases, but still with epiphora and chronic infection of the sac and conjunctiva.

It seems that dacryocystorhinostomy is still the answer to treatment of strictures of the nasolacrimal duct.

348 Jones Ave.

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Case Reports

ADENOIDAL-PHARYNGEAL-CONJUNCTIVAL VIRUS INFECTION WITH ASSOCIATED CORNEAL INVOLVEMENT

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and
TED SUIE, Ph.D., Columbus, Ohio

RECENT reports concerning the new viral disease entity adenoidal-pharyngeal-conjunctival (APC) virus infection indicate that the corneas of affected patients are not significantly involved.[1] However, as the name implies, the virus is capable of infecting three anatomical sites, i. e., adenoids, pharynx, and conjunctiva. Recently Ormsby and associates [2] reported APC-virus-positive cases with corneal involvement in Toronto, Canada. The following case is reported because it further supports the findings of keratitis occurring concurrently in APC-virus infection.

REPORT OF CASE

The patient, a 10-year-old white girl, was first seen in our office on Aug. 31, 1955, complaining of redness and irritation of both eyes, of one week's duration. The symptoms were followed the day of onset by an elevation of temperature (maximum, 104 F). There was a history of frequent swimming in a local pool from which a number of cases of eye infections were allegedly reported. Penicillin ointment locally and tetracycline (Achromycin) orally were prescribed by another physician. After four days the temperature returned to normal. However, the eye signs and symptoms persisted, with some improvement. On first examination (one week after onset) the appearance was that of a typical follicular, nonpurulent conjunctivitis O. U. with mild injection of the globe. There was also a markedly injected, follicular appearance of the lower cul-de-sac and tarsal plate and, to a less degree, of the upper tarsal plate. The most marked feature was many punctate staining areas of the whole cornea in each eye. Tiny refractile spots, which appeared to be subepithelial, were also noted. These were not typical of subepithelial opacities seen in epidemic keratoconjunctivitis. The following day the condition had improved remarkably, with only slight signs of corneal involvement. Complete recovery followed in three days. During the course of this disease there were no complaints of sore throat or other oral involvement. No lymphodenopathy was noted.

Four other patients who had similar follicular conjunctivitis with corneal involvement of this distinct type have been seen during the past two years. These cases were puzzling because the subepithelial opacities were atypical of those found in epidemic keratoconjunctivitis. Also, the disease in these cases differed from the latter in that it was less severe and was of shorter duration. Unfortunately, we did not do viral studies on these four cases because of lack of physical facilities at that time.

LABORATORY STUDIES

Cultures from the eyes of the patient described above were completely negative for both aerobic and anaerobic bacteria as determined with thioglycollate broth without indicator. Small laboratory animals were not injected, since they are not susceptible to the APC virus.[1] Isolation of the APC virus was made from smears taken from the eyes and introduced in tubes containing living HeLa cells. Within three days the cell cultures became granulated, rounded, and then gradually clumped. The culture fluid became acid. These cytopathologic and biochemical changes are characteristically specific of those produced by the APC virus. Neutralization tests revealed that this virus belonged to Type 3.

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Department of Ophthalmology, Ohio State University College of Medicine.

In order to rule out other viral agents, such as those causing psittacosis, epidemic keratoconjunctivitis, herpes, etc., embryonated hen's eggs and mice were inoculated with material from the eyes of this patient. In no instance were changes noted in the mice or in the embryos. Inclusion bodies resembling those in trachoma and inclusion blennorrhea were not demonstrable.

COMMENT

It is difficult to attribute the cause of the keratitis directly to the APC virus, other than to state that no other etiologic agent could be demonstrated. The probability still exists, however, that a concurrent microbial infection, undetected by laboratory studies, was present.

Dr. George Anderson, Ohio State Public Health Laboratories, isolated the virus and performed the neutralizing tests.

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Registry of Interesting Cases

It is the purpose of this section to record cases on the basis of interest only. No complete review of the literature is attempted and no claim for priority is implied except when specifically stated. Publication of case reports is subject to the concurrence of the Editorial Board on the interesting aspects of the case. It is requested that the reports submitted be as brief as is consistent with inclusion of the pertinent facts, bear a title that is as specific as possible, be prefaced by a paragraph that states why the author feels the case is of interest and be accompanied with photographs whenever possible.

ECTOPIC LACRIMAL GLAND

AN UNUSUAL congenital abnormality was discovered when microscopic study was made of a tumor removed from the cornea and limbus of a 23-year-old woman. This case is reported because of the resemblance of the tumor to a dermoid and the rarity of reports of this type of tumor, aberrant lacrimal gland tissue, in the literature.

REPORT OF CASE

The patient was seen in consultation on request of the obstetrics department at Nassau Hospital, Mineola, N. Y. Two finger-like, vascularized conjunctival projections extending on to the cornea of the right eye had been present since birth. Recently, the masses had appeared to become fleshier-looking and to enlarge in size. The upper mass, at 11 o'clock, was 2 mm. wide and encroached upon the cornea 6 to 7 mm. The inferior mass was 4 mm. wide and extended on to the cornea at the 7 o'clock position for a distance of 5 mm. These masses were seen to originate distal to the limbus and beneath the conjunctiva, the upper one being quite red and glandular in appearance. The lower mass did not have this glandular appearance but was also quite red.

Operative Report (Dr. Wendell L. Hughes).—With local anesthesia, the masses which extended on to the cornea were excised with a Graefe knife. The dissection extended into the superficial third of the stroma, and the masses were dissected from the sclera beneath the conjunctiva with a sharp-pointed scissors. The defect in the conjunctiva was closed by bringing the one margin to the limbus and anchoring it there with a mattress suture. The remainder of the defect was closed with a running 000000 chromic surgical mattress suture. At the close of the operation the conjunctiva was in good position and the cornea had been completely cleared of tumor tissue. There remained, however, a yellow line of demarcation deep in the corneal stroma, which was just beyond the furthest extent of the corneal involvement.

Pathology Report (Dr. R. Durham).—Both sections show a well-developed lacrimal gland. In the acini, a few cells have a pale cytoplasm with empty, globular spaces. Most cells have

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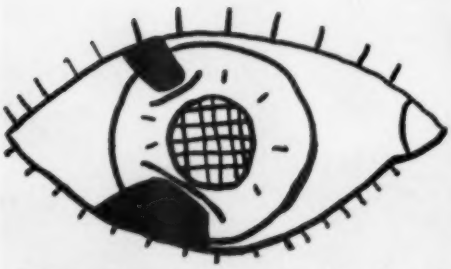

Fig. 1.—Schematic drawing of eye showing position of masses prior to removal.

Fig. 2.—Condition of eye three months following surgery. (From Kodachrome print).

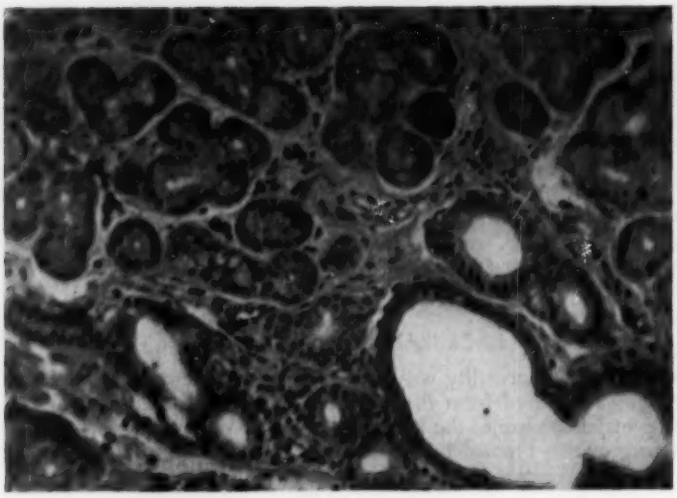

Fig. 3.—Ectopic lacrimal gland (low power).

a reddish-purple, finely granular cytoplasm. The small ducts have two rows of cells. In the outer row the long axes of the oval nuclei are disposed tangentially, and in the inner row they are placed radially. The structure suggests a normal functional gland, and no evidence of presently active hyperplasia. The gland is not compact but is divided into lobules by a delicate connective tissue, lightly infiltrated with lymphocytes.

Diagnosis.—Ectopic or accessory lacrimal gland.

COMMENT

Dame,[1] in 1946, reported the case of a Negro soldier, age 28, with a corneal tumor, first noted in the right eye at the age of 13. The mass was 8 mm. wide, 8.5 mm. long, and 3 mm. high and extended on to the cornea at 7 o'clock for 6 mm. Superior to and parallel to the upper edge of the tumor, and separated by 1 mm. of clear cornea, was an arcuate corneal opacity with some melanin pigment. The tumor was removed with the use of local anesthetic, and the report stated that the tissue consisted of well-formed acini of apparently functioning

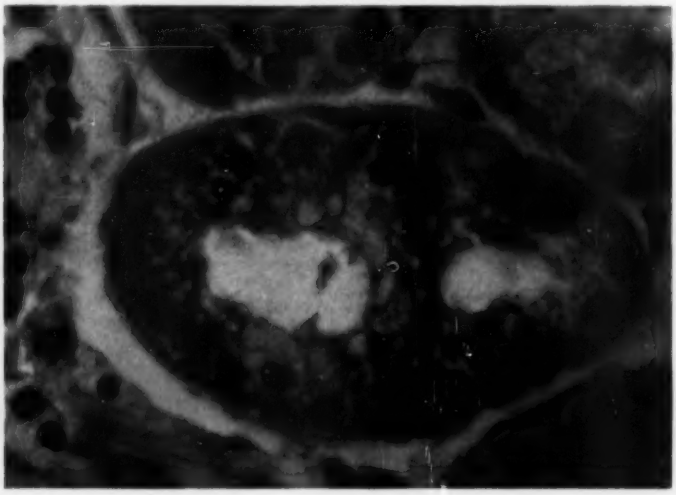

Fig. 4.—Functioning acini of ectopic lacrimal gland (high power).

lacrimal gland. There was no evidence of inflammation or neoplasm. The description of this ectopic lacrimal tissue is remarkably similar to that found in the present case. Boase [2] reported an adenoma of the conjunctiva which was entirely composed of lacrimal tissue, situated between the plica and the limbus, in a 30-year-old African woman.

As far as can be determined, the present report is the second of a corneal ectopic lacrimal gland in the American literature. This condition should be added to those to be considered in the differential diagnosis of corneal and limbal tumors.

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Annual Reviews

CORNEA AND SCLERA

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ANATOMY AND PHYSIOLOGY

GENIS GALVEZ [1] publishes a review of our knowledge of the sympathetic innervation of the cornea and adds a report of his own extensive work. This consists of a microscopic study of the corneas of cat, dog, ox, and man, using various staining techniques. He has demonstrated a rich sympathetic network in the corneal stroma. These sympathetic cords enter the cornea alone or with sensory fibers. Finer fibers originating from these cords anastomose with each other and lie in close relationship to the fixed corneal cells.

Pau [2] has studied the effect of metabolic disturbances of the epithelium and endothelium on corneal permeability and transparency in bovine corneas. He suspects that enzymes within the cornea may play an active role in the transfer of ions and believes that the main factors causing changes of corneal permeability are metabolic changes and damage to the enzyme system.

Of special interest is a paper by Giardini and Gandolfi,[3] who were able to demonstrate that a limbic block with cautery is followed by a decrease in corneal thickness, indicating that there normally is an inflow from the sclera into the cornea.

Sarwar [4] has studied the corneal haze occurring after wearing contact glasses, and he agrees with others that it is due to an imbibition of fluid by the cornea. There is also a loss of corneal sensitivity. He postulates a migration of sodium and potassium ions from the corneal substance into the corneal fluid caused by continued stimulation of the unmyelinated nerve fibers by the contact glass. This ionization presumably produces a rise in the intracorneal osmotic pressure, which causes the cornea to take up fluid. Sarwar has seen corneal edema after the wearing of contact glasses in which the precorneal space is in free communication with air and in which there is no pressure on the aqueous vein. He believes that this observation refutes Ascher's suggestion that edema may be due to a pressure on the aqueous vein, resulting in a back-flow of fluid from the canal of Schlemm into the cornea.

The author has also fitted three eyes in two recent cases of neuroparalytic keratitis with contact lenses containing 2% saline solution with ephedrine, the solution being renewed every two to three hours. The opacity cleared up almost completely.

CORNEAL HEALING AND REPAIR

Wolter and Shapiro [5] have used the "panoptic method" of del Rio Hortega in the study of wound repair in the normal rabbit cornea. This silver-carbonate impregnation of the cells and nerves seems to give a more accurate picture of the histology than other methods. The authors could demonstrate degenerative changes in the fixed cells in less than one hour after incision. Seven days after the injury the consolidation of the wound by parallel rows of elongated fixed cells was complete.

The healing of various types of corneal wounds has been further studied by Aurell,* with special reference to structure and metachromasia. He points out that the interfibrillary substance found not only between the fibrils but completely saturating them is known to be a mucoid, which contains a polysaccharide, "hyaluronosulfuric acid." This substance is intimately connected with corneal transparency. In order to ascertain the presence of mucoid, tissues were stained

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* References 6 and 7.

with toluidine blue, which is practically specific for high-molecular ester sulfuric acids. The author tried to supply a deficiency of corneal mucoid in several ways, but found it impossible to make corneal scars heal with increased transparency. It is explained by the theory that the chemical constitution of the fibril is such as to render it incapable of absorbing metachromatic substance to the necessary extent.

Grawitz [8] likens inflammation of the cornea to inflammation of subcutaneous connective tissue. An alarm reaction is set off by damage to these tissues. Specific foodstuffs are taken up by the tissues, which then form a special breakdown product that he calls *Abbaufaktor*. Plasma transudate combines with this factor, transforming the resting tissue into a reactive inflammatory substance.

Escapini [9] has observed the growth of new nerve fibers into corneal grafts independent of blood vessel growth. Sensation returns in the graft within 12 months and is completely normal in a few years. The nerves have no obvious influence on the transparency of the graft.

A significant paper on corneal healing is contributed by Sigelman, Dohlman, and Friedenwald.[10] These investigators have carefully studied the effect of extirpating various endocrine glands and administering various hormones on wound healing in the rat's corneal epithelium. The needle-puncture technique, previously described by Friedenwald, was used to produce epithelial wounds. They conclude as follows:

1. Hypophysectomy is followed by a diminution in mitotic activity.

2. Cortisone, administered parenterally, causes an increase in the mitotic rate.

3. Local administration of heparin causes a delay in healing.

4. Thyroidectomy, thyroxin administration, parathyroidectomy, adrenalectomy, alloxan diabetes, and corticotropin administration were all without effect on mitotic and wound-healing activities in the rat's corneal epithelium. Similarly, Binder and Binder [11] have shown experimentally in rabbits that the deficiency in fibrin produced by heparin or tromexane interferes with the normal closure and healing of perforating corneal wounds produced by a cataract knife.

The repair of collagenous tissue depends on an adequate intake of ascorbic acid, but the relation of local ascorbic acid concentration to collagenous tissue healing has not been so fully investigated. Boyd,[12] in an attempt to do this, removed the left lens of 20 guinea pigs, and control operations were done on the right eye. While the animals were receiving a known high amount of ascorbic acid, standardized heat injuries were inflicted on the corneas. The aphakic corneas took 40% longer to heal than did the controls. When healing was complete, the ascorbic acid contents of the corneas and the aqueous and vitreous humors were assessed. The ascorbic acid levels of aphakic corneas and aqueous were significantly lower than those of controls. The aphakic vitreous level was only slightly lower. These findings suggest that local ascorbic acid concentrations may be responsible for the rate with which collagen heals.

Cascio and Caselli [13] have investigated the effect of vitamin T (prepared by dissolving 1 gm. of pulverized Torula extract in 20 cc. of distilled water) on wound healing in rabbit eyes. Trephine wounds and keratome wounds were studied under controlled conditions. The vitamin-T-treated wounds healed perhaps 10% to 25% more rapidly than the controls in all animals.

Lange [14] reports various degrees of corneal edema after cataract extraction. After 712 operations, he found that 43 cases deserved consideration. Edema followed 25 times after intracapsular and 18 times after extracapsular extractions. Nine eyes were left with permanent damage. No common denominator was found for all cases.

Cascio [15] has shown (in addition to other effects on the eye) that ultrasonic energy delays the average healing period of corneal wounds in rabbits 23%. These wounds were linear perforating wounds produced by a keratome and superficial circular wounds

produced by a trephine. These observations have been confirmed by Quintieri and Falcinelli.[16]

In addition to their studies on the effect of oxygen on the development of retinal vessels, Michaelson, Herz, and Kertesz [17] have studied the effect of oxygen on the budding of vessels in the adult rabbit cornea. They noted no effect on new-vessel growth into standard thermal burns by increasing the amount of oxygen inhaled. On the other hand, Michaelson, Gluecker, and Stieglitz [18] conclude that low-voltage x-irradiation and cortisone applied topically are equally effective in inhibiting the growth of vessels in rabbit corneas.

Gandolfi [19] removed the corneal epithelium from 18 rabbits. Six were treated with cortisone ointment; six were treated with cortisone and chlorophyll, and six were used as controls. Cortisone alone was found to delay corneal healing, but, when used with chlorophyll, the author found no difference from the healing of the controls.

CHEMICAL INJURIES OF THE CORNEA

In what is to become a systematic investigation of current and newly developed methods of treating chemical injuries of the cornea, Bahn and Allen [20] report on the first substance investigated, namely, calsulfhydryl (Hydrosulphosol). This was selected for early evaluation because of its relative newness as a therapeutic agent and because of the wide difference of opinion as to its clinical value. A special standardized technique was developed using albino rats as test animals. In a series of four experiments in which rat eyes were burned with 0.1 N hydrochloric acid and treated with several forms of calsulfhydryl, the drug proved to have no beneficial effect. In another series of four experiments in which rat eyes were burned with 1.1 N sodium hydroxide and treated similarly, the drug proved to have either no beneficial effect or a definitely deleterious effect.

Browning and Lippas [21] report two cases of what they call pHisoHex keratitis, a chemical keratitis caused by accidentally instilling a small quantity of this preoperative cleansing agent in the conjunctival sac. This substance, pHisoHex (pHisoderm with hexachlorophene), is widely used as a bactericide. Both patients sustained a severe superficial keratitis with edema of the entire cornea, which persisted for several months, until complete healing and clearing of vision resulted. In dogs and rabbits, pHisoHex caused even severer corneal damage: epithelial loss and a deep keratitis, with swelling and sloughing of the corneal endothelium. The component of pHisoHex causing corneal damage is trinitrotoluene (Entsufon; Triton), a sulfonated ester.

Hartmann [22] reports the case of a girl whose corneas were severely burned by tear gas (chloroacetophenone). Deep corneal infiltrations resulted, which ultimately cleared completely.

Further application of edathamil calcium-disodium EDTA (Versene) for calcium deposits in the cornea is reported by Breinin and DeVoe.[23] The authors have used it with complete success in 10 cases and recommend a corneal bath of a 0.01 or 0.05 M solution for 15 to 20 minutes. An iontophoresis cup can be used with benefit. Oksala,[24] too, has given further confirmation to Grant's treatment of calcium deposits in the cornea with edathamil. He found it effective experimentally in steer eyes, as well as in human eyes.

ULCERATIVE AND NONULCERATIVE KERATITIS

Pseudomonas Infection.—Spencer [25] has carefully reviewed the literature on Pseudomonas aeruginosa infections of the eye and done some significant laboratory studies on the effect of polymyxin B, and hyaluronidase plus polymyxin B, on this infection in the corneas of rabbits. Carefully controlled experiments proved that polymyxin B prevented ulceration completely if used early enough and markedly diminished the spreading of a well-established ulcer. Hyaluronidase added to the preparation had no effect. Moorman and Harbert [26] report two early cases of corneal ulceration due to P. aeruginosa cured by combined topical and parenteral polymyxin B therapy. Good vision was pre-

served in both patients. They also review the literature since 1922 and analyze the 58 cases in which adequate data are available. The disappointing visual results following these infections ever since the advent of polymyxin are probably due to delay in starting adequate therapy.

Corneal Erosion.—Popp [27] reports a group of 17 patients who developed large corneal erosions after using a polyethylene glycol ester for some minor ocular infection. Ophthalmic ointments containing this glycol ester appear to be extensively used. Presumably, the anesthetic quality of the substance is responsible.

In the treatment of recurring erosions, Fleischanderl [28] reports better results after cauterization with 20% zinc sulfate than after iodine. He reports 22 patients successfully treated.

Lagophthalmos.—Kettesy [29] has given us a rather lengthy general discussion of lagophthalmos, in which he discusses the value of local applications, moist-chamber glasses, tarsorraphy, levator tenotomy, conjunctival flaps, and orbital decompression. Proper emphasis seems to have been placed on these different techniques.

Herpes Simplex Corneae.—MacKneson and Ormsby [30] have continued their important studies on the virus of herpes simplex and have recently reported on the effect of various antibiotics on this virus. They used their own laboratory strain of virus and first determined its pH stability, which they found to lie between 4.0 and 10.0. Herpes-infected mouse brain was emulsified according to their special technique; various antibiotic solutions were added, and, after incubation for four hours, dilutions of this mixture were injected intracerebrally in mice. The only antibiotics used in their experiments which had an inhibiting effect on the herpes simplex virus were chlortetramycin (Aureomycin) and puromycin.

This work confirms the original experiments of Braley and Alexander in which the herpes simplex virus was inhibited by chlortetramycin borate in concentrations of 5.0 and 2.0 mg/cc. Although recent observers have not confirmed the early reports of clinical response to this antibiotic in human herpetic infection, these in vitro studies nevertheless suggest that chlortetramycin is the antibiotic of choice if one wishes to use one. The concentration of antibiotics used in these in vitro experiments exceeded the levels usually obtained in body fluids but were comparable to those used in collyria and ointments. The authors conclude, further, that tetracycline (Achromycin), chloramphenicol (Chloromycetin), erythromycin, and carbomycin (Magnamycin) in a concentration of 2.0 mg/cc. had no effect on the titer of the virus suspension. Puromycin in concentration of 2.0 mg/cc. had a slight inhibitory effect on the virus.

The effect of some new antibiotics on experimental herpetic keratitis has been studied by Boles-Carenini and Cambiaggi.[31] They found that none of the following substances used topically had any prophylactic or curative effect: gramicidin with neomycin, erythromycin, chloramphenicol, tetracycline, carbomycin, or sulfisoxazole (Gantrisin). Paternostro [32] reports improvement in 8 of 12 cases of herpetic infections of the eye after giving paraaminobenzoic acid 6 gm. daily by mouth and 2 gm. daily intravenously.

Epidemic Keratoconjunctivitis.—The subject of epidemic keratoconjunctivitis has received notable attention during the past years in the form of a summary article by Cockburn.[33] The author reviews our knowledge on this subject, especially since 1941, when it was fully treated by Hogan and Crawford. Cockburn gives a splendid review of the entire subject, including the history of the disease, its clinical description, laboratory studies, and epidemiology. Those points which now seem to be clear have been listed as follows:

1. Epidemic keratoconjunctivitis is a worldwide disease of considerable potentialities.

2. In the United States it seems to be epidemic, being spread either in association with eye clinics or among people living in intimate contact with one another. At times it becomes epidemic in industrial plants,

where a large proportion of the cases occur in workers exposed to minor eye injuries.

3. A satisfactory strain of the causal agent is not available in this country, and little fundamental work on the epidemiology of the disease can be done until one is produced.

4. Prevention of transmission of infection in eye clinics is a responsibility of both ophthalmologists in practice and persons responsible for the maintenance of first-aid stations in industrial plants. A special responsibility falls on the larger eye clinics associated with medical schools, for an epidemic in such a place might spread infection over the whole country.

5. The large epidemics radiating from industrial plants could be explained by available data. The initial infection might be introduced to the first-aid clinic of the factory and the infection then transmitted to patients attending for minor eye ailments; the patients would carry the infection to their homes, and their families would, in turn, develop the disease.

Cockburn and Danielson [34] give an excellent description of four recent cases. One primary case was followed by three secondary ones. The secondary ones were treated with serum from the primary case, but no definite conclusions could be drawn. The authors are hopeful, however, that immune sera with higher antibody titer may become available and useful in the treatment of this disease.

Ormsby and Fowler [35] give a report on serological observations on patients who contracted epidemic keratoconjunctivitis during the Windsor, Ontario, epidemic, in 1951. The sera from 61 patients failed to show neutralizing antibodies to the Sanders-Braley strain of virus. These workers did isolate five strains of virus, but these proved to be strains of mouse encephalitis virus, closely related to the Theiler TO strain. It is of interest that the use of cortisone increased the incidence of paralysis and death in mice inoculated from both test and control cultures.

Other experiences with epidemic keratoconjunctivitis are reported from abroad. Kassner [36] reports 110 cases occurring in one summer in West Germany. He recommends ascorbic acid and cyanobalamin U. S. P., which seem to aid in clearing the infiltrates.

Junker [37] reports excellent results in the treatment of epidemic keratoconjunctivitis with acetylcholine ointment alone or in combination with an antibiotic. It would seem that this treatment deserved further investigation.

Mycotic Infections of the Eye.—Pautler, Roberts, and Beamer [38] report a case of corneal ulcer, hypopyon, and iridocyclitis from which they cultured Monosporium apiospermum and in which they found the same organism in the histological sections after enucleation. They report this case as the first instance of corneal ulcer and intraocular infection associated with a species of Monosporium. Sulfonamides and antibiotics were not effective. Fazakas [39] describes 34 cases of ocular keratomycoses, 20 of the primary and 14 of the secondary type. Of the 20 primary cases, 11 were superficial, 7 deep, and 2 transitional. Except for two cases caused by Aspergillus flavus, all the infections were benign and healed readily.

A comprehensive review by Valentin Gamazo [40] on the treatment of infected ulcers of the cornea has appeared during the past year. Although no new material is given, it is an excellent monograph, with 82 references.

CORNEAL DISTURBANCES ASSOCIATED WITH METABOLIC OR SYSTEMIC DISEASES

Arcus Senilis.—Arcus senilis is the subject of a monograph by Forsius,[41] published as a supplement to *Acta ophthalmologica.* It represents a major work on this subject and includes 156 references. The author has developed the subject from its historical background and studied the correlation between arcus and fat metabolism with the aid of the old, and especially the new, methods available. The ratio of cholesterol and phospholipids was slightly higher for persons with arcus than for those without. In young persons, arcus is associated with extensive lipidochemical alterations in the blood serum,

as is not true in elderly persons. In the latter group, the author believes that local senile changes in the cornea are mainly responsible for arcus.

Keratoconjunctivitis Sicca. — Sjögren [42] has found only 14 cases of complete lacrimal deficiency and keratoconjunctivitis sicca in the literature. He lists three possible causes of congenital absence of tears, as follows:

1. Aplasia of the secretory cerebral nuclei or of the secretory nerve paths. This is frequently associated with paralysis of the ocular muscles, and the condition has been demonstrated microscopically by Huebner.

2. Aplasia of the lacrimal glands. Although this theory has not been substantiated, cases of congenital xerostomia have been reported in which there was congenital alacrimia. Aplasia of the salivary glands has been demonstrated in this condition.

3. Persistence of a state physiological at birth. The first to suggest this possibility was Sommer (1903), although Darwin was the first to point out that infants do not secrete tears when crying. The time varies at which tear secretion starts; Darwin found the maximum delay to be 139 days. Sjögren appears to be the first to have measured the secretion of tears in newborn infants. The Schirmer II method was used without previous anesthesia. Of premature infants, about 40% had a lacrimal secretion of 0-5 mm. Sjögren also measured the secretion of 49 full-term infants. Considering the borderline of normal reflex tearing in adults to be 15 mm., 80% of all newborn infants had subnormal lacrimal secretion. In 12% it was almost entirely lacking and remained so for at least one week. Sjögren considers this alacrimia pathological only if it persists beyond the neonatal period. In two cases of persistent congenital alacrimia with no other symptoms, in which microscopic examinations were made, the lacrimal glands were found to be entirely normal. Sjögren is of the opinion that some of the cases of keratoconjunctivitis sicca reported in adults who have had deficient lacrimal secretion since early childhood in reality belong to the category of persistent congenital alacrimia.

By extirpating the lacrimal gland in rabbits, Nover [43] was able to produce a condition similar to human keratoconjunctivitis sicca. Regeneration of the lacrimal gland was striking and was accompanied by an improvement in the corneal disease.

X-ray examination of the parotid gland (sialography) after iodized oil U. S. P. (Lipiodol) injection is used routinely by Parret [44] in patients with keratoconjunctivitis sicca. He reports the following abnormal findings: dilatation of Stensen's duct, reduction in number of terminal ducts, and retention of iodized oil, sometimes for several months. Parret has made four classifications of sialograms, depending on the degree of parotid gland destruction. The test may have both diagnostic and prognostic value.

The value of hormone therapy in Sjögren's disease is still the subject of some controversy. Gurling, Bruce-Pearson, and Pond [45] treated six patients with corticotropin, and three were given cortisone in addition. No increased tearing resulted, even though normal gland tissue was present, as proved by biopsy. The fact that the arthritic symptoms were relieved by this therapy suggests to the authors that there may be a difference in the etiology. In six rather mild cases, Gaulhofer [46] found only slight symptomatic improvement following the use of cortisone. No improvement was noted in severe cases, and Gaulhofer considers this form of treatment useless. Eadie and Thompson [47] treated 12 patients with cortisone and corticotropin. Cortisone eye drops satisfactorily relieved symptoms in most cases. Hydrocortisone did not appear to be more effective, nor did the addition of cortisone eye ointment confer any extra benefit. Systemic cortisone and corticotropin similarly benefited these patients, but the authors conclude that their use is not warranted in the treatment of this condition. Sealing the lacrimal puncta relieved the severer cases, making cortisone treatment unnecessary. Salvi,[48] too, has used diathermocoagulation of the lacrimal canaliculi in eight

patients with Sjögren's disease. All were successful, although two required a second operation.

Scleromalacia Perforans.—An excellent review of scleromalacia perforans and allied diseases has been made by François,[49] who had the opportunity of studying the histology of one eye. The results of his pathological examination coincided with those of others.

The effect of hormone treatment of the accompanying arthritis on scleromalacia perforans raises the question as to whether the cortisone and corticotropin are beneficial or detrimental to the scleral disease. In a patient with rheumatoid arthritis, Mathias [50] reports scleromalacia perforans coming on during prolonged treatment with corticotropin and cortisone. Gjessing,[51] on the other hand, reports the case of a man operated on at the age of 69 for cataract of his left eye. At 82 years of age he returned with scleromalacia perforans of both eyes and rheumatoid arthritis. He was then treated with topical cortisone, with seemingly good results. The author speculates on the cause of this disease and draws an analogy between scleromalacia perforans and osteomalacia in pregnant women. He therefore suggests that, in addition to cortisone, sufficient amounts of calcium, phosphorus, and vitamin D be given.

Progressive Scleroperikeratitis.—This disease has been suggested as another collagen disease by Manschot.[52] He gives the clinical and histological findings in a patient who had anterior segment inflammation for 30 years. The eye in his case is described as "an ivory-colored disc which filled the entire entrance to the orbit."

Band Keratopathy.—Leira [53] has added 4 cases of hypercalcemia and band keratopathy to the 55 cases previously reported. His well-documented report points out several interesting facts. More than one-half of the known cases were due to intoxication with vitamin D (35 cases); 8 had hyperparathyroidism; 6, Boeck's sarcoid, and 10 were reported as due to other causes. In 41 of the total number (59) there was associated renal disease. All four of Leira's cases were caused by toxic doses of vitamin D; three patients were children under 5 years of age. Two of them were siblings. The author points out that the doses of vitamin D which cause keratopathy vary considerably. Even 1,600,000 units given during a period of 11 days caused a well-marked keratopathy in a 32-year-old man. Leira also found that three of his four patients showed regression of the ocular disease. Slight conjunctival changes regressed entirely within three weeks, and corneal changes showed marked clearing within three months. Conjunctival deposits disappeared completely even when the serum calcium remained high, while corneal deposits persisted for months and years after serum calcium had been normalized.

Folk [54] reports a well-studied case of band keratopathy, including pathological examination. The condition was associated with renal disease (polycystic kidney), the commonest accompaniment or cause of this type of keratitis.

Gifford and Maguire [55] report a case of vitamin D intoxication following the daily ingestion of 150,000 U. S. P. units for two years. Reversible corneal opacities occurred, which the authors say are indicative of impending renal damage.

Two cases of calcification in the sclera without ulceration are reported by Gartner and Rubner.[56] Both patients had hypercalcemia, as the result of taking large doses of vitamin D. The eyes of one patient were examined at autopsy. They showed scleral nodules in varying stages of resolution with calcification.

Cystinosis with Corneal Changes.—Cases of this unusual condition continue to be reported. Bürki [57] adds another case, that of a one-year-old infant, to his series. The disease represents a disorder of the amino acid metabolism resulting in cystinuria and deposition of cystine crystals in the conjunctiva and cornea. Schiff [58] reports the same findings in a 2½-year-old boy.

Ochronosis.—Seitz [59] reports on biopsy of tissue from the conjunctiva in the case of a 70-year-old man with ochronosis. He

had typical corneal and conjunctival pigmentation in the interpalpebral zone. The biopsy showed pigment granules in the connective tissue without cellular reaction around them.

Ichthyosis.—Franceschetti and Maeder [60] describe what they believe may be a new form of corneal dystrophy or sign of ichthyosis. It occurred in a young man with congenital ichthyosis. Fine, bluish, and translucent filaments were visible just in front of Descemet's membrane. The condition did not resemble any of the three forms of corneal disease in ichthyosis described by Cordes and Hogan in 1939. Friedman [61] describes what he believes may be a new form of keratitis associated with ichthyosis. There were innumerable circular grayish opacities in the posterior stroma; the greatest number were located centrally, where the opacities extended forward halfway through the parenchymal thickness. Peripherally they diminished markedly in thickness. There was no appreciable loss of vision. Ichthyosis is more commonly associated with the formation of irregular opacities in the superficial corneal stroma, accompanied by changes in the corneal nerves.

Phlyctenular Keratitis.—Yagihashi [62] has studied 60 cases of phlyctenular keratoconjunctivitis by slit lamp and biopsy. Ulceration of a phlyctenule occurs only after lymphocytes replace the polymorphonuclear leucocytes. He supports the theory that a tuberculin-like reaction takes place.

Tuberculous Scleritis. — Chrzanowzka-Srzednicka [63] treated 17 patients who had a presumptive diagnosis of tuberculous scleritis with isoniazid (0.05 gm. doses three times a day). The average total amount given was 8 to 9 gm. Streptomycin and aminosalicylic acid were used in addition. The results were said to be excellent.

Pemphigus.—Although ocular pemphigus (essential atrophy of the conjunctiva) usually occurs without generalized pemphigus, it is occasionally associated with the latter. A single report by Martínez Barrios, Malamud, and Alvarez Arbo [64] describes a patient with both ocular and generalized pemphigus. Adequate treatment with both corticotropin and cortisone failed to cure the condition. This result conforms with the majority of previous reports.

Keratoconus.—Numerous articles of considerable interest dealing with this important and interesting condition have appeared in the past year. Mihalyhegyi [65] has continued his researches on the nature of keratoconus, with special attention to the curvature of the anterior segment. He employs molds of the living eyes, which are photographed and enlarged. Contrary to the accepted belief, he finds that the anterior sclera participates in the development of the cone.

Rossi [66] has summarized our present knowledge of the condition and its relation to keratoglobus.

Keratoconus has at times been thought of as anterior glaucomatous cupping. In order to study any possible relationship between keratoconus and glaucoma, Cascio [67] investigated the effect of provocative tests for glaucoma in nine patients with keratoconus. Since all tests were negative, he concluded that no connection exists between the two diseases.

Guimarães [68] adds a case of posterior keratoconus to the six previously reported. In this condition the posterior corneal surface has a curvature greater than normal, and greater than the anterior corneal surface. The thin, disc-like formation in the center of the cornea is surrounded by an opaque areola.

Acute keratoconus, presumably due to rupture of Descemet's membrane, is said to be rare, although Rohrschneider and Stohr [69] state that it occurs in 11% of all cases of keratoconus. They observed five such cases within one year at the clinic in Munich. The rupture occurred toward the end of the disease and led to scarring and flattening of the cone, and therefore to final improvement in vision.

King [70] describes the development of keratoconus in two women at 39 and 27 years of age who had had thyroidectomy for thyrotoxicosis 14 and less than 1 year before,

respectively. He discusses the role that thyroid dysfunction might play in the development of this corneal condition, without coming to any definite conclusion.

Cambiaggi [71] describes four cases in which keratoconus was associated with retinitis pigmentosa. Three of the patients were siblings, and the fourth had a sister who also had retinitis pigmentosa. All had retinitis since birth; the keratoconus became apparent between the 10th and the 18th year of age. Stress is laid on the hereditary factor in this condition.

Keratoplasty seems to be the definitive treatment of choice for keratoconus. Walser[72] reports eight patients with keratoconus treated by keratoplasty. Six grafts remained clear. The author advocates operation as a final therapeutic measure when vision is less than 1/15. He uses a 6 mm. trephine, direct sutures, and a contact glass for fixation.

Pterygium.—The literature on pterygium has not been as extensive during the past year as during the two preceding years. Kamel [73] gives an interesting historical review of the three best-known theories regarding the cause of pterygia; namely, the neoplastic, the degenerative, and the inflammatory. His extensive experience with the treatment of this condition, so common in Egypt, has led him to a standard treatment. This consists essentially of lamellar keratectomy of the local area and careful dissection of all tissues under the pterygium, with excision of the entire mass and cauterization of the bed with phenol. No sutures are used. Cortisone and antibiotics are used after surgery.

Two rather similar operations have been described by Sie-Boen-Lian [74] and by Krwawicz.[75] In severe and recurrent cases Sie-Boen-Lian uses the "bare-sclera" technique, in which the head of the pterygium is buried in a rectangular scleral pouch. Krwawicz describes his surgical technique as follows: After mobilization of its head, the pterygium is planted in a scleral pouch, made by a vertical incision in the sclera 6 mm. behind the limbus. He claims excellent results with no recurrences. Fritz [76] reports an unusual case of blindness (V. O. D., 2/400; V. O. S., 4/400) caused by pterygia. The patient was a 61-year-old full-blood Eskimo. Transplantation of the three pterygia found failed to improve his vision.

UNUSUAL DISEASES AND CONDITIONS

Bowen's Disease.—Evidence seems to be accumulating that irradiation after surgery is the treatment of choice for intraepithelial epitheliomas of the cornea. A case of Bowen's disease of the corneal limbus is reported by Mascati.[77] Radical surgery followed by deep x-irradiation was used, with good result. The author believes that after such surgery only one-quarter of the amount of radiation previously reported is necessary.

Myxofibromata of Cornea.—Wales[78] noted four independent tumors, entirely in the cornea, at birth. They were located near the outer and the inner limbus of each eye. The tumors recurred after surgery. The diagnosis was microscopic.

Corneal Crystals.—The appearance of various crystals seen in the cornea has been well described by Delong and Dolenek.[79] Brockhurst, Hynes, and Cogan [80] describe an unusual case of crystalline dystrophy of both corneas in which no hereditary tendency could be traced. Di Ferdinando,[81] on the other hand, reports the case of a 10-year-old boy with bilateral symmetrical superficial corneal opacities consisting of shiny, radially placed needles. Vision was 5/10. The father had primary fatty degeneration of both corneas. The author believes these two heredofamilial corneal degenerations are transmitted by the same gene, even though morphologically different.

Ophthalmia Nodosa.—Corkey [82] describes an interesting case of ophthalmia nodosa due to caterpillar hairs, with pathological study by Ashton. No previous case has been reported from Ireland, and only two have been reported by British authors.

Examination Aids and Methods.—Appelmans and Hendrichs [83] employ Wood's ultraviolet light to detect preclinical pingueculae.

They describe a white sheathing of the conjunctival vessels at the site of the future pinguecula. The hyaline degeneration, with hypertrophy of elastic fibers, might be the result of a special sensitivity to sunlight.

MEDICAL THERAPY

Cortisone and Corticotropin.—These drugs continue to occupy the most prominent position in ophthalmic literature as far as the therapeutic agents are concerned. Glowing reports of the usefulness of cortisone in interstitial keratitis continue to appear, but other reports would lead one to believe that its usefulness has been overrated.

Oksala [84] has examined 35 patients with syphilitic interstitial keratitis at least one year after the termination of the active stage of the disease. Ten had been given an average dose of 6,000,000 units of procaine penicillin. Fourteen had been given penicillin (average, 9,000,000 units) associated with malaria (average, 10 chills). In addition to this combined treatment, cortisone was administered topically to the remaining 11 patients. He summarizes his observations as follows: There is as yet no specific remedy for syphilitic interstitial keratitis. Penicillin has no effect on the course of the disease. Fever therapy reduces the subjective and objective symptoms of the disease, as it does in other intraocular inflammations and is, therefore, of use in the active stage of the disease. Oksala believes that it is premature to evaluate fully the usefulness of corticotropin and cortisone. His experience indicates that, although a rapid improvement is often seen through hormone administration, the improvement is not very lasting. Vannas' † experiences with topical cortisone at the Helsinki University clinic indicate rather promising results in interstitial keratitis but warn that maintenance doses should not be discontinued too early. On the basis of five patients treated with cortisone locally plus penicillin and fever, Segal and Zylo-Filipowicz [85] conclude that cortisone has only a symptomatic benefit. The signs and symptoms returned when cortisone was discontinued.

A more optimistic point of view regarding the treatment of interstitial keratitis with cortisone is given by North,[86] who describes 20 cases of syphilitic interstitial keratitis, 8 in detail. He states that the use of cortisone has changed this disease from a long, painful illness, resulting in defective vision or blindness, to an acute one, lasting only a few days. If treatment is started early enough, no corneal scarring need follow. Horne,[87] too, obtained excellent immediate and long-term results in the treatment of 26 eyes with syphilitic interstitial keratitis.

Lian and Lian [88] report dramatic cures of interstitial keratitis in Indonesian natives by topical use of cortisone. They also report very favorable results after its use in Westhoff's keratitis, a similar disease, which may be related to nummular keratitis (Dimmer).

Mitsui and Hanabusa [89] describe four cases of hypopyon keratitis due to a fungous infection and one case due to Pseudomonas infection. All cases followed topical use of cortisone or hydrocortisone.

Fibrin Film.—Weisser [90] reports on the use of thromboplastin in chemical burns, abrasions, and corneal ulcers. It is easily applied, relieves pain, and promotes healing. Further confirmation of the value of fibrin film in the treatment of corneal ulcers of almost any kind is offered by Cuendet and Michels.[91] They report particularly good results in abrasions, in burns, and even in herpetic keratitis.

Streptokinase-Streptodornase.—Portfolio[92] reports on the use of streptokinase-streptodornase in the treatment of severe corneal ulcers. Streptokinase is thought to act as a catalyst, causing the transformation of a zymogen or normal human blood (plasmogen) into a proteolytic enzyme (plasmin). Plasmin is capable of digesting fibrogen and lysing fibrin. Streptodornase is an enzyme which supposedly hydrolyzes deoxyribonucleic acid and deoxyribose nucleoprotein, which together constitute 30% to 70% of

† Vannas, S., in discussion on Oksala.[84]

the sediment in thick, purulent exudates. Thus, streptokinase-streptodornase theoretically aids in the treatment of ulcers where débridement might be of value.

Portfolio treated 14 patients with topical application of 10% streptokinase-streptodornase in methylcellulose solution. Antibiotics and supportive treatment are also used. Although the author's results were not remarkably good, he suggests that streptokinase-streptodornase might be of value in severe corneal ulcers.

Perilimbal Procaine Block.—Fridman [93] reports good results in the treatment of herpetic keratitis after using pericorneal injections of procaine. Of 21 patients with superficial keratitis, 18 were improved; and of 5 with deep keratitis, 4 were improved.

Iontophoresis.—Iontophoresis may be one of our somewhat neglected therapeutic tools. Erlanger [94] writes of his extensive experience with this treatment, which includes 30 years of experience, many thousands of experiments in animals, and 100,000 iontophoresis treatments. He claims that iontophoresis with calcium chloride (3:1000) and physostigmine salicylate (0.03:10,000), in the amount of 1 ma. for 15 minutes, can clear a perfectly cloudy vitreous temporarily. Physostigmine with acetylcholine acting as a vasodilator is said to be effective in amblyopia ex anopsia. Acetylcholine is also used successfully in the treatment of extraocular muscle paralysis. His results in the treatment of iritis and corneal ulcers are less spectacular.

SURGICAL THERAPY

Keratoplasty.—Several important statistical reports have been published. Paton [95] has given us an excellent analysis of his great experience in corneal grafting, which comprises 365 operations in 330 eyes. A total of 299 cases were followed for two months or longer; 193 grafts (64.5%) remained clear. The percentage of clear grafts in various diagnostic groups were tabulated as follows: keratoconus, 89.3%; Groenouw's dystrophy, 85.7%; nonspecific scarring, 68.8%; scarring from inactive ulcer, 66.7%; interstitial keratitis, 62.2%; leucoma, 55.6%; active ulcer, 50%; trachomatous scarring, 45.5%; chemical burns, explosion injuries, and traumatic wounds, 39.1%; adherent leucoma, 35.3%, and Fuchs' dystrophy, 30.8%. Paton states that, although not all cases lend themselves to exact prognostic classification, a definite prognosis can be given in a high percentage of cases, thus avoiding many useless operations. Of his patients, 72.1% obtained visual improvement after operation; 20.7% had the same vision as before operation, and 5.9% had reduced vision following operation. A total of five enucleations were performed; 54 of the 365 grafts were lamellar grafts.

Paton also gives a well-illustrated description of his operative techniques. Circular grafts cut by trephine were used throughout. An overlying basket-type suture was used in grafts 6 mm. or less in diameter. Direct sutures were used in larger grafts.

Fine [96] reports visual results of 100 partial penetrating keratoplasties; 74% of patients had improved vision, and 41%, 20/40 or better. The best results were in patients with keratoconus, Groenouw's dystrophy, and disciform keratitis. Poor results were obtained in dense vascularized scars and chemical injuries.

Esente [97] reports his results in 24 cases in considerable detail. One corneal abscess occurred behind the graft, and one traumatic cataract resulted from perforation of the anterior chamber during operation. His best results follow operation on the avascular cornea. The author advised use of β-radiation both before and after operation. He emphasizes its usefulness as a preliminary treatment before perforating keratoplasty.

Franceschetti [98] gives an excellent review of corneal grafting from his extensive personal experiences. The three methods now in use—namely, the perforating graft, the lamellar graft, and the so-called "mushroom" graft—are each given careful consideration. Franceschetti outlines his technique and indications for each procedure, with special emphasis on the less commonly used "mushroom" graft. He finds it applicable to cases

in which perforating or lamellar grafting is doomed to failure and therefore recommends its use in cases of serious burns, aphakias, and Fuchs' epithelial dystrophy.

Pittar,[99] of Auckland, New Zealand, reports on a seven-year experience in corneal grafting. His results have been uniformly good and his technique is simple. His success is attributed in part to his corneal splint and trephine guide, which he has described previously.

Techniques in Keratoplasty.—Thomas,[100] whose interest in corneal grafting over the past 30 years is well known to all, has summarized his ideas of fixation of corneal grafts. His article should be read by all ophthalmologists who do this specialized surgery. Many principles employed today result directly from his early experimental work, such as (1) fixation of the graft with crossed sutures, (2) shelving or sloping margins, (3) use of trephines of different size, the smaller trephine being used for removing the graft, and (4) prevention of the formation of a fibrinous coagulum by the use of citrated saline solution.

Thomas uses interrupted marginal sutures in large grafts 6 or 7 mm. in diameter and has accepted Filatov's egg membrane as part of his normal routine.

Friede[101] presents a paper on his technique based on a large experience. He carefully preserves Descemet's membrane in leucomas and pays special attention to any preexisting glaucoma.

In addition to the many complications of keratoplasty mentioned above, Salleras[102] gives an excellent review of the whole subject.

Many interesting individual reports continue to appear. Günther[103] describes a 76-year-old patient who had seven penetrating keratoplasties, after which the cornea remained clear. The keratitis was caused by a severe bilateral ocular rosacea. One eye required five antiglaucoma operations in addition. This case would seem to be an all-time high. A patient who developed a hernia of the choroid was successfully treated by scleral grafting by Sivasubramaniam.[104] The use of direct penetrating grafts for scleral defects may not have received sufficient attention.

Experimental Keratoplasty.—Kitagawa[105] gives what appears to be a realistic report of his experiences with keratoplasty in rabbits. In normal corneas 18 to 24 grafts remained clear. Only 10 of 22 grafts remained clear when the host's cornea was faintly nebulous. In another group, of 15 rabbits, whose corneas had leucomas due to chemical burns, no grafts remained clear. Kitagawa finds that in his experience a clear margin of the original cornea is essential for success in grafting. In a second study, of the preservability of corneal tissue in vitro, he found that the cornea must be used within 24 hours after removal from the donor eye.

Hervouet, Stanković, and Blagojević[106] have made several interesting observations on the fate of scleral grafts in cornea. Histological and microchemical evidence indicates that the grafts are completely replaced by new tissue resembling cornea. Descemet's membrane did not regenerate in their grafts, though both epithelium and endothelium reformed in a fairly normal manner.

Preservation of Cornea by Dehydration.—McNair and King[107] were able to remove the entire cornea in the cat and, after preserving it by the glycerin-saline method with freezing and drying in vacuo, obtained clear lamellar grafts.

Plastic Corneas.—Stone[108] reports progress in his work on interlamellar plastic artificial discs since his last report, in 1952. Openings have been maintained in the anterior corneal layer in apposition to interlamellar plastic discs in several rabbits longer than previously reported. He has not yet been able to explain some irregularities in his results and does not feel that this operation is ready for human application.

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Obituaries

JAMES W. SMITH, M.D.
1893-1955

With the passing of Dr. James W. Smith, on Oct. 24, 1955, ophthalmological circles have lost a spirited and enthusiastic leader.

Born in Washington, D. C., May 16, 1893, he was graduated from New York University College of Medicine in 1917. He served as the president of the alumni association in 1939-1940.

After World War I service as a lieutenant in the Army Medical Corps, Dr. Smith began his career as an eye surgeon in 1919 at the old Post Graduate Hos-

JAMES W. SMITH, M.D.
1893-1955

pital, to which he remained affiliated for his professional life—namely, 36 years—attaining the standing of Attending Ophthalmologist and Clinical Professor of Ophthalmology at New York University-Bellevue Medical Center. He was chief of the eye service at the Hospital for Joint Diseases and Consulting Ophthalmologist at Goldwater Memorial Hospital. He was a Fellow of the American College of Surgeons and the New York Academy of Medicine and served as chairman of the eye section of the Academy in 1951-1952. He was a charter member of the New York Society for Clinical Ophthalmology and served as its president in 1941-1942.

Jim Smith led a full life. He was fortunate in being one of those who was happiest at his work. Clinical ophthalmology was his forte. This, together with his love of teaching, made his course in "Practical Pointers in Office Practice" a popular one at the American Academy of Ophthalmology.

Those of us who were fortunate enough to work under him received operative principles by example. He would tolerate no breaks in the perfect handling of human tissues and flawless instrumentation.

He was influenced by Martin Cohen and James White, both of whom he worked with. Such contributions as "Ochronosis of the Sclera and Cornea Complicating Alkaptonuria" were the reflection of his former teacher, and "Medical Significance of Ocular Torticollis" and "The Problem of Strabismus in Childhood," that of his latter teacher.

His avocation was the collection of historical manuscripts—the gathering of early American autograph letters with medical and ophthalmological interest. He accumulated autographs of every president of the United States. He was a director and charter member of the Manuscript Society, formed as the National Society of Autograph Collectors in 1948.

His friendly spirit emanated from him, and he had an intimacy with hundreds of professional men, who felt close when accosting him as Jim.

His interest in scientific programs never wavered, and he was sure to be found at the stated meetings. This proclivity for keeping abreast of current topics plus his good judgment made him the prefect counselor and adviser on questions of procedure.

He is survived by his widow, Sara Pollack Smith, and their son, Dr. Barry F. Smith.

"Green be the turf above thee,
Friend of my better days!
None knew thee but to love thee,
Nor named thee but to praise."

ISADORE GIVNER, M.D.

News and Comment

PERSONAL NEWS

Faculty Appointment, University of Georgia School of Medicine.—Dr. John R. Fair has been appointed Assistant Professor of Surgery and Chief of Ophthalmology at the University of Georgia School of Medicine, Augusta.

Dr. Fair received his bachelor degree from the Loyola University in Chicago in 1937, and was awarded his M.D. degree from Loyola University College of Medicine, Chicago, in 1941. Following his internship at Jackson Memorial Hospital, Miami, Fla., he served a three-year residency in ophthalmology in Army hospitals, after which he was appointed Assistant Director of the Ocular Research Unit, Walter Reed Army Medical Center, Washington, D. C. In 1954, Dr. Fair served as Chief of the Eye Section of the Army's 98th General Hospital in Germany. It was from this post that he resigned, with the rank of Lieutenant Colonel.

Dr. Fair is certified by the American Board of Ophthalmology, a member of the American Medical Association, a fellow of the American Academy of Ophthalmology and Otolaryngology, a fellow of the American College of Surgeons, and a member of the Association for Research in Ophthalmology.

Appointment of Dr. Derrick T. Vail.—Dr. Derrick T. Vail, editor-in-chief of the *American Journal of Ophthalmology*, has been appointed to the National Advisory Neurological Diseases and Blindness Council for a term of one year. His appointment was announced today by Surgeon General Leonard A. Scheele, of the Public Health Service, U. S. Department of Health, Education, and Welfare. He will serve the unexpired term of the late Dr. Jonas S. Friedenwald of Baltimore.

Dr. Vail is one of the nation's leading ophthalmologists and has played an important role in the growth and development of ophthalmology in this country. With his appointment, he becomes one of the 12 Council members who advise the Surgeon General on an important part of the research program of the National Institute of Neurological Diseases and Blindness at Bethesda, Md.

Appointment of Dr. Alson E. Braley.—Dr. Alson E. Braley, head of the Department of Ophthalmology, Iowa State University, has been appointed chairman of the Ophthalmology Training Grant Committee, National Institute of Neurological Diseases and Blindness of the National Institutes of Health. A distinguished teacher, Dr. Braley will direct and develop a training program in ophthalmology, to reduce the shortage of clinical teachers and investigators through grants made to teaching institutions. The current supply of teachers, research workers, and clinicians is seriously inadequate to meet the required needs for training in this field.

Annual Charles H. May Memorial Lecture.—Dr. Edwin B. Dunphy will deliver the annual Charles H. May Memorial Lecture, sponsored by the Section of Ophthalmology of the New York Academy of Medicine. The lecture will be given at the Academy on March 19, 1956. The subject will be "Radioactive Isotopes in Ophthalmology."

ANNOUNCEMENTS

New York Society for Clinical Ophthalmology.—The Society announces a participating conference, to be held at The Waldorf-Astoria Hotel, New York, Friday and Saturday, April 13 and 14, 1956. Registrants will be able to participate in seminars on various subjects. The discussions will be led by prominent members of the Society. Subjects will include glaucoma, biomicroscopy, therapeutics, muscles, and neuro-ophthalmology.

Registration is limited to 100. Fee $35, luncheons included. A detailed program will be sent to registrants. Communications may be addressed to the registrar, Miss Gloria Benabo, 737 Park Ave., New York 21.

SOCIETY NEWS

The Eastern New York Eye, Ear, Nose & Throat Society.—The 194th meeting of the Society was held Nov. 10, 1955.

The meeting divided in the afternoon into the Eye and the Ear, Nose, and Throat sections. Many important and interesting cases were shown and discussed in both sections.

The subject discussed in the Eye Section was "Trends in Ophthalmology in the Field of Refraction." Dr. A. E. Sloane, Professor of Refraction at Harvard University, presented the cases.

Wills Eye Hospital.—The Eighth Annual Clinical Conference of the staff of Wills Eye Hospital and the Wills Eye Hospital Ex-Resident Society will be held at the Hospital on Feb. 17 and 18, 1956. The Bedell Lecture will be delivered by Dr. A. D. Ruedemann, of Detroit, on "Progressive Bilateral Exophthalmos: Differential Diagnosis and Treatment."

The program will also include scientific papers by members of the staff and ex-residents of the hospital, technical exhibits, and a color television program sponsored by Smith, Kline & French Laboratories, which will present ocular surgery, case presentations, and demonstrations of procedures and techniques.

On Friday evening, Feb. 17, there will be an informal reception and supper for the ophthalmologists and their wives. On completion of the two-day program, the Wills Eye Hospital Ex-Resident Society will hold its annual meeting and dinner at the Union League, Philadelphia, on Saturday, Feb. 18, at 6:30 p. m.

Correspondence may be addressed to I. S. Tassman, M.D., Wills Eye Hospital.

Association for Research in Ophthalmology.—The 1956 meeting of the Eastern Section of the Association for Research in Ophthalmology will be held in New York on Saturday, April 28, at Columbia University College of Physicians and Surgeons, 630 W. 168 St. All those interested are invited to attend the scientific sessions of these meetings.

The Association for Research in Ophthalmology is an open society. Membership in the Association is not a prerequisite for presenting a paper which has been accepted by the Program Committee.

Titles and abstracts of papers to be presented at the spring 1956 meeting will be received until Feb. 28, 1956. It is hoped that each presentation can be limited to 10 minutes in order to save time for discussion. Publication of papers presented at this meeting is not required. The abstracts should be sufficiently informative to permit a good arrangement of the program. Abstract forms will be sent on request.

George K. Smelser, local chairman, 630 W. 168 St., New York 32.

North Carolina Eye, Ear, Nose, and Throat Society and South Carolina Society of Ophthalmology and Otolaryngology.—Arrangements have been completed for next year's joint meeting of the North Carolina Eye, Ear, Nose, and Throat Society, and the South Carolina Society of Ophthalmology and Otolaryngology. Headquarters will be the George Vanderbilt Hotel, Asheville, N. C., and the dates Sept. 17, 18, and 19, 1956. The following otolaryngologists will be on the program: Dr. L. R. Boies, Minneapolis; Dr. J. M. Converse, New York, and Dr. W. G. Hardy, Baltimore.

The following ophthalmologists will participate in the program: Dr. Harold W. Brown, New York; Dr. Harold Scheie, Philadelphia, and Dr. Byron Smith, New York. An unusually attractive program has been arranged, and we are anticipating a large attendance.

Latin Society of Ophthalmology.—The second meeting of the Latin Society of Ophthalmology will be held in Madrid on April 24 to 28, 1956. The convention is to be presided over by Prof. Dr. Buenaventura, Dr. H. Arruga, Dr. Diaz Caneja, and Dr. Lopez Enrique. Dr. Perez Llorca will take part, Dr. C. Costi acting as secretary and Drs. L. Mier, Carreras Matas, and M. Aguilar Bartolomé as assistant secretaries.

The topic to be dealt with concerns the "Use of Acrylic Material in Ophthalmology," with suggestions on "Orbital Implantations" by Dr. Arruga (Barcelona), "Surgical Application to the Lacrimal System and Eyelids," by Prof. Dr. Bietti (Parmi), and "Application to the Eyes," by Prof. Paufique (Lyons), in collaboration with Prof. Dr. Strampelli (Rome) with respect to the intracameral acrylic lens. Dr. (Mme) Ferrer Faisan (Habana, Cuba) will discuss "Contact Lenses," and Dr. (Mme) Legrand (Nantes), "Intracorneal Plastics."

Communications concerning these topics, as well as applications for registration, should be addressed to the secretariat, 10 Paseo del Ray, Madrid, before Feb. 29, 1956.

Registration fee is 500 pesetas for ophthalmologists, and 400 pesetas for each person accompanying them. The fee should be sent to the secretariat upon registration.

Omaha and Council Bluffs Ophthalmological and Otolaryngological Society and Nebraska Academy.—Thursday, March 15, 1956, the Omaha and Council Bluffs Ophthalmological and Otolaryngological Society and the Nebraska Academy of Ophthalmology and Otolaryngology are holding a joint all-day session in Omaha. The principal speaker for ophthalmology will be Dr. Harold G. Scheie, of Philadelphia, and the principal speaker for otolaryngology will be Dr. George Shambaugh Jr., of Chicago. Members of the neighboring eye, ear, nose, and throat societies have been invited, and the Kansas City Society of Ophthalmology and Oto-Laryngology has made plans to attend as a group.

GENERAL NEWS

Pathological Laboratories Available for Processing Eyes.—Since 1950 the pathological laboratory at Marquette University Medical School has been processing eyes for pathological study, and it could readily handle 25 to 50 more eyes a year.

Leslie Dana Medal.—Under the terms setting up the annual award of the Leslie Dana Medal, the National Society for the Prevention of Blindness has responsibility for selecting each year's recipient after submitting five nominations to the St. Louis Society for the Blind for consideration. As recommended by the St. Louis Society, the selection of Mrs. Helenor Wilder Foerster, San Francisco, one of the five candidates proposed for the 1955 award, was unanimously approved.

National Society for the Prevention of Blindness.—The Society announces the availability of grants-in-aid for basic laboratory or clinical research projects that may add to an understanding of the etiology of blinding eye diseases or improve methods of diagnosis, treatment, or prevention.

To be considered, applications should be received before April 1, 1956. Forms may be obtained from the Research Committee, National Society for the Prevention of Blindness, 1790 Broadway, New York 19.

In December, the National Society reported new research grants amounting to $12,200. These were allotted to the following:

Dr. Gordon E. Gibbs, University of Nebraska College of Medicine, Omaha, $4,000, for studies of the adrenocorticoid function in relation to diabetic retinitis

Dr. Jerry Jacobson, New York Eye and Ear Infirmary, $1,500; electrophysiology of the eye

Dr. Irving H. Leopold, Wills Eye Hospital, Philadelphia, $2,500; choroidal circulation

Drs. A. Gerard DeVoe and Robert S. Coles, New York University Postgraduate School of Medicine, $1,900; use of pancreatic Dornase in inflammatory ocular infections

Dr. Daniel G. Vaughan Jr., University of California School of Medicine, San Francisco, $300; evaluation of antibacterial agents against Pseudomonas aeruginosa

Dr. Peter C. Kronfeld, Illinois Eye and Ear Infirmary, Chicago, $2,000; cardiovascular effects upon the human tonogram

Annual Scientific Session, Brooklyn Eye and Ear Hospital Alumni Association.—The Brooklyn Eye and Ear Hospital Alumni Association wishes to announce its Fifth Annual Scientific Session. It will be held at the Brooklyn Eye and Ear Hospital on Saturday, April 7, 1956.

The program that has been arranged is as follows:

Ophthalmology

Dr. Ralph I. Lloyd	Glaucoma in 1900
Dr. Willis S. Knighton	Medical Treatment of Glaucoma
Dr. Harold G. Scheie	Surgical Management of Glaucoma
Dr. Daniel Kravitz	Gonioscopic Significance in Glaucoma Surgery

There will be a motion picture symposium on the following topics:

Surgical Treatment of Glaucoma: Goniotomy and Goniopuncture in Treatment of Congenital Glaucoma.....Dr. Harold G. Scheie

Cataract in Glaucoma (loaned through the courtesy of Dr. Wendell L. Hughes)

Otolaryngology

Dr. Philip Meltzer	Surgical Treatment of Deafness
Dr. N. Lagoumis	A Series of Case Reports of Peripheral Facial Nerve Paralysis
Dr. Salmon Harvey	Physical Aspects of Hearing and Equilibrium as Applied to the Human Ear
Dr. L. A. Peer	Plastic Surgery of Malformations of the External Ear
Dr. Irwin Fine	Differential Diagnosis and Treatment of External Ear Disease

National Council to Combat Blindness, Inc.—The National Council to Combat Blindness, Inc., 30 Central Park South, New York 19, in accordance with its program primarily engaged in the financing of research in ophthalmology and its related sciences, announces its 1955-1956 awards for grants-in-aid and fellowships, as approved by its Scientific Advisory Committee:

GRANTS-IN-AID

Retina Foundation, Boston; Endre A. Balazs, M.D. (Continuation; $3,800): Synthesis of Hyaluronic Acid in the Vitreous Body of Embryos and Young Animals

New York University—Bellevue Medical Center, New York; Goodwin M. Breinin, M.D. ($2,300): Electromyography of the Extraocular Muscles Including Stimulation Studies and Evaluation of Drug Effects on the Action Currents

State University of Iowa, Iowa City; Hermann M. Burian, M.D. (Continuation; $500): Studies of the Human Electroretinogram

New York Medical College, Flower and Fifth Avenue Hospitals, New York; Benjamin Friedman, M.D. ($1,250): The Identification of Lens-Dissolving Enzymes in Aqueous Humor and Lens

New York Hospital—Cornell Medical Center, Dan M. Gordon, M.D. ($4,000): Application of Visual Aids in Patients with Subnormal Vision

University of California at Los Angeles; S. Rodman Irvine, M.D., and Robert Brunish, M.D., ($4,550): Hyaluronic Acid and Hyaluronidase in Ocular Tissue

New York Eye and Ear Infirmary, New York; Jerry Hart Jacobson, M.D. (Continuation; $2,100): Electroretinography in Retinal Diseases

University of California, Francis I. Proctor Foundation, San Francisco; Samuel J. Kimura, M.D. (Continuation; $2,000): Study of Keratitis Sicca and Sjögren's Syndrome

Wills Eye Hospital, Philadelphia; Harry Green, Ph.D., and Irving H. Leopold, M.D. ($4,500): Intraocular Tension and Bicarbonate Concentration in Animal Eyes

State University of Iowa, Iowa City; P. J. Leinfelder, M.D. (Continuation; $1,971): Effect of Change in pH in the Aqueous on Metabolism of the Lens

Hadassah-University Hospital, Jerusalem; I. C. Michaelson, M.D. (Continuation; $2,470):

1. Factors Affecting New Vessel Growth in the Cornea
2. Changes in Hyaluronic Acid Content of Vitreous in Physiological and Pathological Conditions

Kumamoto University Medical School, Japan; Yukihiko Mitsui, M.D. (Continuation; $600): Cultivation of Trachoma Virus in Cultivated Human Cells

University of Oxford, Nuffield Laboratory of Ophthalmology, England; Antoinette Pirie, Ph.D. ($2,000): Study of Changes in the Constituents and Metabolism of the Lens During Development of Cataract

Tulane University of Louisiana School of Medicine, New Orleans; J. William Rosenthal, M.D. ($600): A Genetic and Ophthalmic Study of a Family Showing Acromegaly, Unusual Abnormalities of the Skin, and Corneal Dystrophy

Columbia University College of Physicians and Surgeons, New York; George K. Smelser, Ph.D. (Continuation; $1,500): Investigation of Experimentally Produced Exophthalmos

Manhattan Eye, Ear and Throat Hospital, New York; C. C. Teng, M.D. (Continuation; $1,000): Optic Nerve Study

Okayama University Medical School, Japan; Jun Tsutsui, M.D. ($1,000): Clinical and Virological Studies on Trachoma, Especially Immunity, Spontaneous Cure, and Tumor-like Nature of the Infected Tissue

Biophysics Research Laboratories, University of Pittsburgh; Jerome J. Wolken, Ph.D. (Continuation; $2,600): Photoreceptor Structures

Institute of Ophthalmology, University of London, England; Alan Woodin, Ph.D. ($1,800): Clarification of the Cause of Resistance to Outflow of the Aqueous Humour with Particular Reference to Simple Glaucoma

Full-Time Research Fellowships

Edgar Auerbach, M.D., Harvard University, the Biological Laboratories; George Wald, Ph.D., Director, Direct Supervisor ($4,800): Color Vision, Dark and Light Adaptors

Norman I. Krinsky, Ph.D., Harvard University, the Biological Laboratories; George Wald, Ph.D., Director, Direct Supervisor ($3,600): Esterification of Vitamin A by Tissue of the Eye

Ralph Levine, M.D., New York University—Bellevue Medical Center; Goodwin M. Breinin, M.D., Director of Research, and A. Gerard DeVoe, M.D., Chairman, Department of Ophthalmology; Direct Supervisors ($3,600): Use of Radioactive Isotopes in Ophthalmology

Part-Time Research Fellowship

Albert B. Chatzinoff, M.D., Mount Sinai Hospital, New York; Frederick H. Theodore, M.D., Acting Chief, Department of Ophthalmology, Direct Supervisor ($1,500): Chronic Deficiency of 1-cis Vitamin A as the Possible Etiology of Retinitis Pigmentosa

Summer Fellowships

Donald Able Berman, Tulane University of Louisiana School of Medicine, New Orleans; James H. Allen, M.D., Chief, Department of Ophthalmology, and Marion A. Guidry, M.D., Direct Supervisors ($600): Studies on the Electrophoretic Properties of Soluble Corneal Proteins

Arthur Berken, Washington University School of Medicine, St. Louis; Bernard Becker, M.D., Chief, Department of Ophthalmology, Direct Supervisor ($400): Effect of Cortisone Administration on the Cells of the Islets of Langerhans and the Capillaries of the Pancreas

George Contis, Biophysics Research Laboratory, University of Pittsburgh; Jerome J. Wolken, Ph.D., Director, Direct Supervisor ($400): Studies—Drosophila Melancaster

Carl Gates Freese Jr., M.D., Massachusetts Eye and Ear Infirmary, Boston; David G. Cogan, M.D., Direct Supervisor ($400): Evaluation of the Syndrome Known as "Spasm of the Near Reflex"

Barbara B. Green, University of California; Phillips Thygeson, M.D., Direct Supervisor ($600): Cytology of the Aqueous in Experimental Uveitis

Arthur Robert Kallmann, University of California; Michael J. Hogan, M.D., Direct Supervisor ($600): Histologic Studies of Aqueous Drainage into the Canal of Schlemm

Charles A. Perera, M.D., is the newly elected chairman of the Scientific Advisory Committee and will serve in this capacity for a two-year term.

Irving H. Leopold, M.D., director of research and attending surgeon at Wills Eye Hospital, Philadelphia, and chairman of the department of ophthalmology of the Graduate School of Medicine, University of Pennsylvania; and Bernard Becker, M.D., professor and head, department of ophthalmology, Washington University School of Medicine, St. Louis, have been added to the Scientific Advisory Committee of the organization. Other members are as follows:

James H. Allen, M.D., Chief
Department of Ophthalmology
Tulane University of Lousiana School of Medicine
New Orleans

Alson E. Braley, M.D., Director
Department of Ophthalmology
State University of Iowa
Iowa City

Arthur G. DeVoe, M.D., Chief
Department of Ophthalmology
New York University—Bellevue Medical Center
New York

Louis B. Flexner, M.D., Professor
Department of Anatomy
University of Pennsylvania School of Medicine
Philadelphia

Dan M. Gordon, M.D., Asst. Prof. of Clinical Surgery
Department of Ophthalmology
New York Hospital—Cornell Medical Center
New York

Charles Haig, Ph.D., Professor
Department of Physiology
New York Medical College, Flower & Fifth Avenue Hospitals
New York

Michael J. Hogan, M.D., Director
Francis I. Proctor Foundation
University of California School of Medicine
San Francisco

Peter C. Kronfeld, M.D., Professor
Department of Ophthalmology
University of Illinois College of Medicine
Chicago

A. E. Maumenee, M.D., Director
Department of Ophthalmology
Johns Hopkins Hospital & University
Baltimore

Karl Meyer, M.D., Associate Professor
Department of Biochemistry
Columbia University College of Physicians and Surgeons
New York

Stuart Mudd, M.D., Professor
Department of Microbiology
University of Pennsylvania School of Medicine
Philadelphia

Lorrin A. Riggs, Ph.D., Professor
Department of Psychology
Brown University
Providence, R. I.

Samuel L. Saltzman, M.D., Associate Professor
Department of Ophthalmology
New York Medical College, Flower and Fifth Avenue Hospitals
New York

Kenneth C. Swan, M.D., Director
Department of Ophthalmology
University of Oregon Medical School
Portland, Ore.

Phillips Thygeson, M.D., Professor
Department of Ophthalmology, Francis I. Proctor Foundation and University of California Medical Center
San Francisco

Applications for 1956-1957 grant-in-aid and fellowship awards (full-time) will be considered at the Seventh Annual Meeting of the Scientific Advisory Committee, to be held in June, 1956. Closing date for receipt of completed applications for these awards is April 15, 1956.

Applications for summer student fellowships will be reviewed in advance of the meeting, and such applications should be filed with the office of the organization no later than April 1, 1956.

All applicants for fellowships, full-time or summer, are required to make their own arrangements for suitable research facilities with accredited institutions.

Appropriate forms may be obtained by addressing the Secretary, National Council to Combat Blindness, Inc., 30 Central Park South, New York 19.

Books

The Visual Fields. By Brodie Hughes. Price, $7.50. Pp. 174, with 158 illustrations. Charles C Thomas, Publisher, 301 E. Lawrence Ave., Springfield, Ill., 1954.

It is a unique experience to find a book on visual fields written by a neurosurgeon, and surprising to find that the author himself took all of the fields therein reported. If one adds to this the fact that the material presented is an extremely valuable contribution to the science of perimetry, we have in this publication real book news. The author describes his methods of doing quantitative perimetry and has correlated the fields he has personally taken with the pathological anatomy found at operation or autopsy.

It is obvious that the greatest value of the book lies in the field of intracranial pathology, where the author is thoroughly at home, and no one who is interested in neuro-ophthalmology can fail to find these chapters of great value.

The author stresses the fact that quantitative perimetry brings out the three types of field loss: local loss of vision at the field periphery, loss of vision within the field periphery, and depression of vision, which may be local or generalized. The peripheral loss of the field typically known as "coast-erosion" type is important to recognize, since it occurs in relatively few conditions, such as tabes, injury, secondary optic atrophy, retinitis pigmentosa, some forms of toxic amblyopia, and hysteria. "Its identification will, therefore, reduce the diagnostic possibilities considerably. Consideration of the history, fundus changes and associated signs will usually suffice to identify the final cause."

The author points out that in depression defects in any part of the field the rate of progress of the lesion may be determined by the slope of the depression. When this is gradual, the central isopters being severely affected and the peripheral ones but little, the lesion is usually active and progressing rapidly. Other items of interest are the following:

Peripheral loss of the field in patients with papilledema is frequently associated with a centrocecal scotoma arising from the peripapillary edema, and some of the scotoma may break through to the periphery of the field, thus producing a combination of central and peripheral field loss.

In the author's experience, the description of the exact distribution of the nerve fibers in the disc which best fits clinical experience is that of Posner and Schlossman, who postulate that all fibers coming from the retina nasal to a vertical line drawn through the fovea go to the nasal side of the disc and all those from the temporal side to the corresponding side of the disc. The fibers from the retina between the disc and the fovea also run to the upper and lower portions of the nasal disc, a distribution which explains some of the curious field defects found with lesions of the nerve head, especially glaucoma.

The macular fibers make up about half the bulk of the fibers of each optic nerve, so that small, precise lesions of the nerve may give rise to scotomas not unlike those derived from retinal lesions. The explanation of the vulnerability of the papillomacular bundle seems to rest on a special blood supply anatomically separate from that supplying the rest of the nerve. The nerve fiber bundle type of defect commonly seen in lesions of the optic nerve is likewise due to the fact that individual bundles of fibers in the optic nerve have their own special blood supply; hence vascular diseases, such as arteriosclerosis, are likely to produce nerve fiber bundle defects in the fields.

Although binasal hemianopsia has been attributed in the past to displacement outward of the chiasm or optic nerves against the carotid or anterior cerebral arteries, recent investigations have shown that this is very seldom the case, most such field defects being examples of secondary optic atrophy following papilledema.

In addition to the localizing information given by perimetry, the author believes that the pathological nature of the lesion is often hinted at, and that "individual lesions betray themselves by the general character of the field defect and its evolution and behavior. Each type of lesion, pituitary tumor, aneurysm, arteriosclerosis, etc., tends to assume a characteristic pattern in its behavior by reason of its position or origin and mode of development. It is by studying these behavior patterns . . . that the individual lesion may be identified."

No criticism can be made of this book because of the scant treatment given conditions like glaucoma, where field changes are so important, for the author expressly states that it is not intended to give a description of glaucoma field beyond that which will enable the neurologist to distinguish it from other types of field.

It is significant that this book appears just after the death of Traquair, who served as a constant guide and inspiration to the author. Hughes not only has carried on in Traquair's tradition, but has made an equally valuable original contribution. This book should be in the library of everyone who sees neurological cases.

Neuroglia: Morphology and Function. By Paul Glees. Price, $5.00. Pp. 111, including index and bibliography, with 44 illustrations. Charles C Thomas, Publisher, 301 E. Lawrence Ave., Springfield, Ill., 1955.

Neuroglia, or glia, has generally been regarded as a supporting tissue comparable to other organs. Boll, in 1874, was the first to show that neuroglia and connective tissue differ fundamentally in both development and staining reactions. Since then many papers have appeared on the subject of neuroglia. This book summarizes all of this work, including the author's own contributions to date. Two main forms of neuroglia are distinguished, the macroglia, consisting of two types of cells, protoplasmic and fibrous astrocytes, and the oligodendroglia and microglia.

Recent studies have shown that glial cells and fibers are not rigid structures with unalterable patterns, but that the microglia cells may change into ameboid elements and that macroglia can proliferate. Tissue cultures, according to Glees, "demonstrate motility of all cells cultivated from neural tissue. For this reason the static conception may not hold good for the living state, and glia cells, or at least their processes, may change their position, increasing or decreasing their sphere of influence."

The author suggests that neuroglia forms are not merely protective, insulating and supporting structures for the central nervous system, but exercise metabolic influences exceeding the metabolic requirements of the tissue itself. The fact that oligodendroglia cells, particularly astrocytes, are connected to blood vessels, suggests the possibility of a metabolic function, which the author suggests should be further explored. Although of no direct interest to clinical ophthalmologists, those who are interested in neuro-ophthalmology in particular will find this book an authoritative source for information regarding neuroglia.

The Lacrimal System: Clinical Application. By Everett R. Viers. Price, $7.50. Pp. 159, including index, with 73 illustrations. Grune & Stratton, Inc., 381 Fourth Ave., New York 16, 1955.

There is always a distinct need for an authoritative book on any part of the eye. This is particularly true regarding the lacrimal system, since so much has been written in the last 50 years and so many diversified points of view have been expressed. Many years ago, when this reviewer asked a famous professor of ophthalmology how he should treat patients who complained of epiphora, the answer was, "Send them to your nearest competitor." These patients are still

very troublesome, but Dr. Viers has produced a very informative and practical book which combines in one volume many important papers, together with his own experience. The material is well organized, beautifully illustrated, and with a good bibliography following each chapter. Through the consultation of this book, at least some patients will be salvaged from the group who eventually find their way into the hands of "the nearest competitor" and will still be welcome in the office.

Kinships of Animals and Man: A Textbook of Animal Biology. By Ann H. Morgan, Ph.D., Price, $6.75. McGraw-Hill Book Company, Inc., 330 W. 42d St., New York 16, 1955.

No man can become an ophthalmologist, or at least a good one, without having an intense interest in the natural history of the animals and plants around us. This constitutes the field of biology, too often made horrific, or at least dull, by poor teaching. For those who have maintained after college an enduring interest in living things, and for those whose inherent interest in biology was dulled by poor pedagogy, this book will be a source of much pleasure. The author, a professor of zoology at Mount Holyoke College, has approached her task of teaching biology from a philosophical point of view—that there is a unity throughout the universe of plants and animals, and that by exploring the kinship in both function and structure of plants, animals, and man, one may obtain a better understanding of life and the patterns of evolution. Although the book must, naturally, present facts, these are so artfully and interestingly presented that further exploration of the book becomes a pleasure instead of a bore. There is no part which is beyond the intellectual horizon of any well-trained physician, and, while reading it may not make one more perfect in the extraction of a cataract, it will certainly increase his mental stature as a physician.

The first part of the book deals with the problems of matter and energy as they occur in plants and animals, and includes a discussion of atoms and molecules and the chemical theory in general. There follows a discussion of the cell and its behavior, as a single unit and when combined to form tissues and organs. In the chapters on ecology the association of animals and plants, their competitions, and unconscious cooperations are given an interesting treatment, and, finally, the story of evolution is expounded as a story of the continuity of life.

There are lots of books which lie just outside the solar system of ophthalmology which are fun to explore, and this is one of them.

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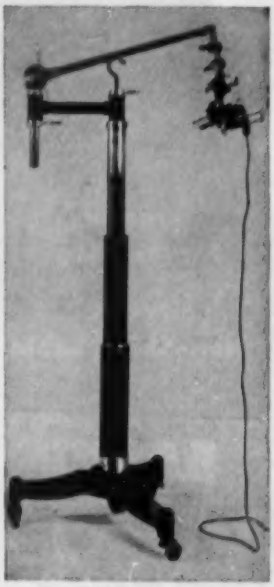

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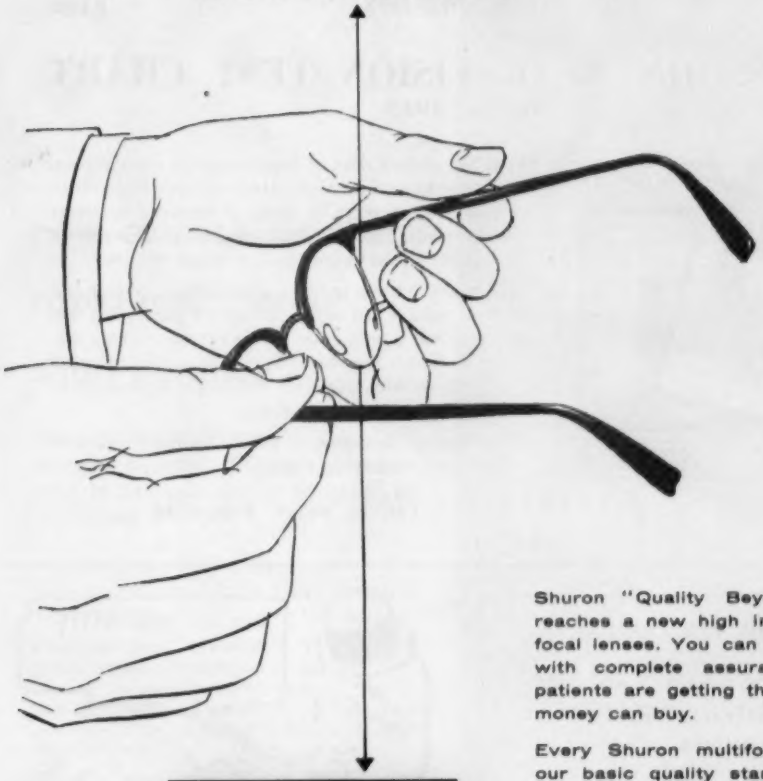

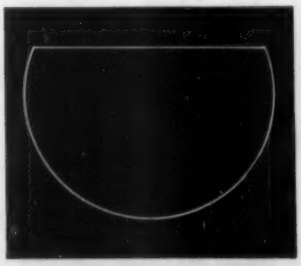

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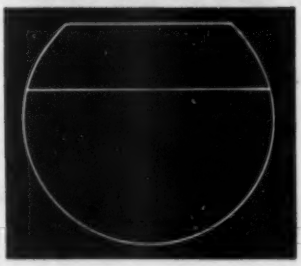

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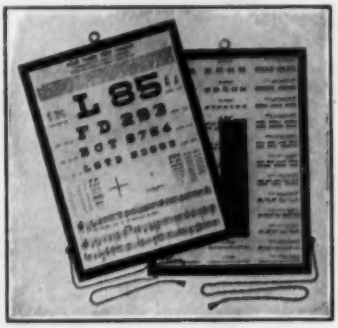

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*Schlegel, H. E., Jr., and Swan, K. C.: A. M. A. Arch. Ophth. *51*:463 (May) 1954.

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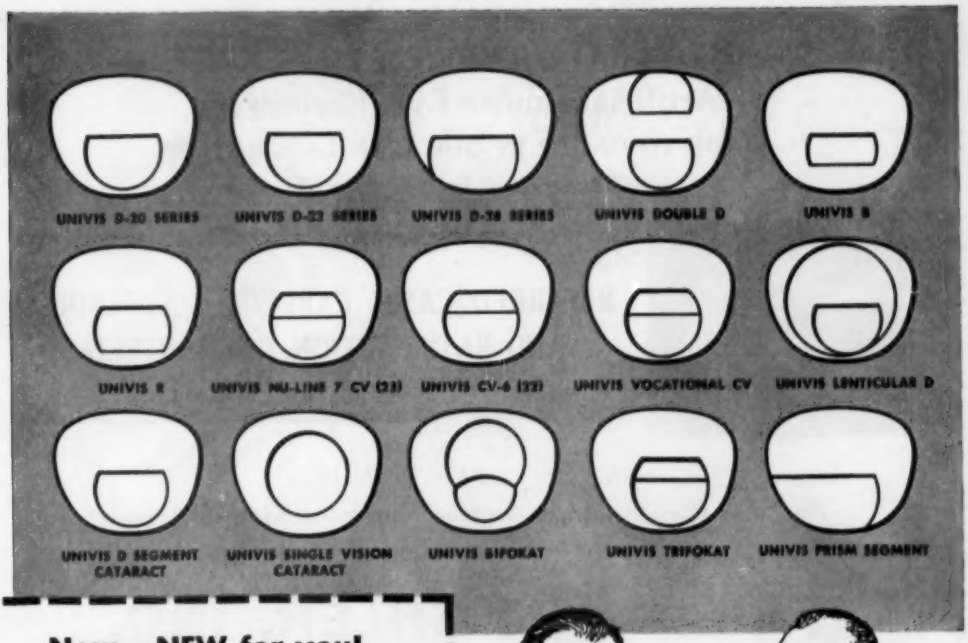

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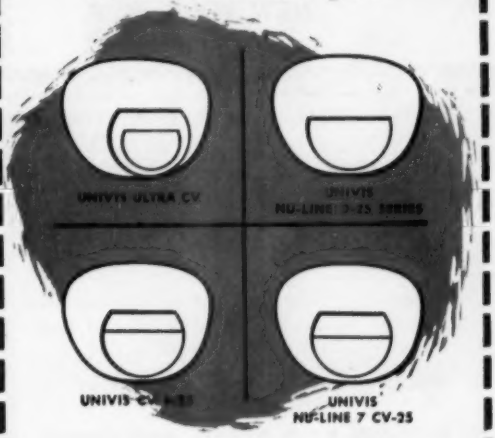

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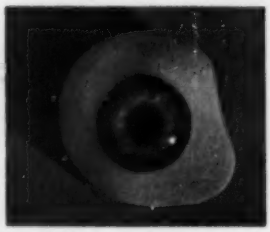

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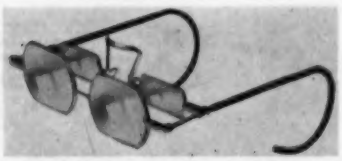

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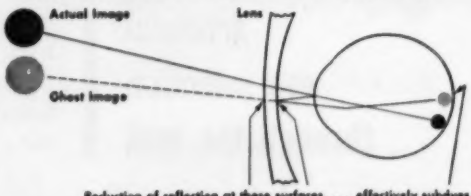

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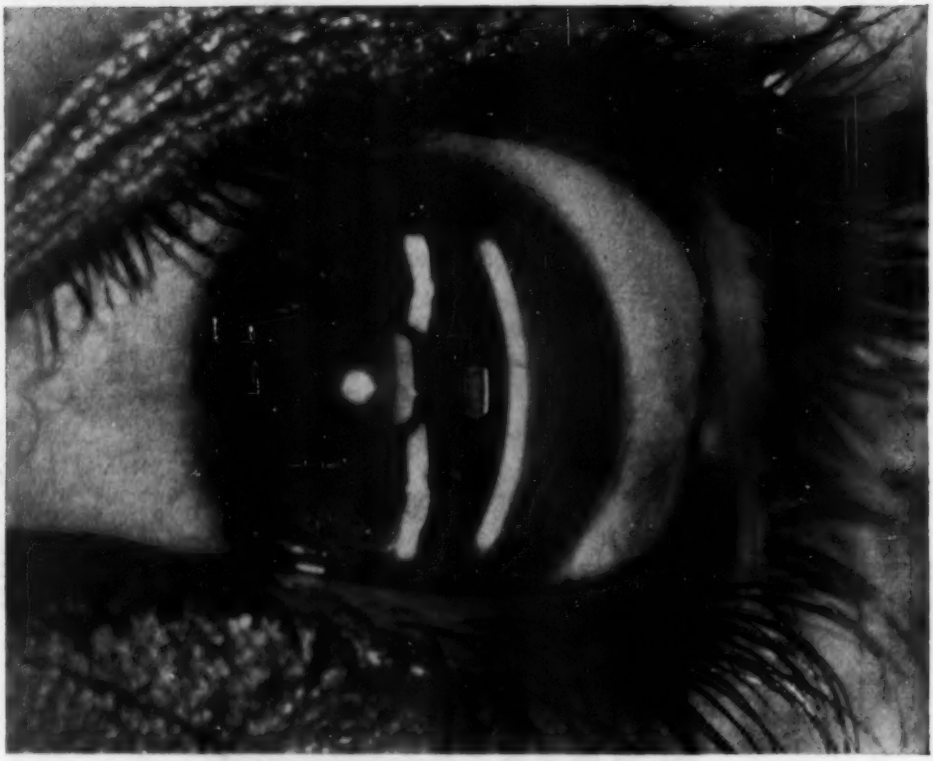

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